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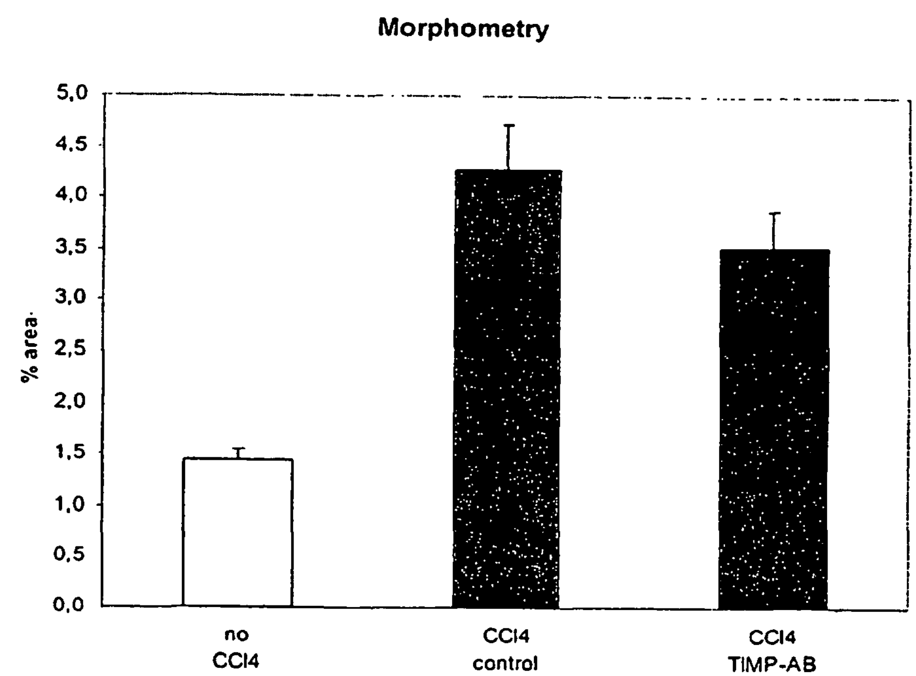
(54) Title: HUMAN TIMP-1 ANTIBODIES



(57) Abstract: Human antibodies that bind to TIMP-1 can be used as reagents to diagnose and treat disorders in which TIMP-1 is elevated, such as liver fibrosis, alcoholic liver disease, cardiac fibrosis, acute coronary syndrome, lupus nephritis, glomerulosclerotic renal disease, benign prostate hypertrophy, colon cancer, lung cancer, and idiopathic pulmonary fibrosis.

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HUMAN TIMP-1 ANTIBODIES

[01] This application claims priority to and incorporates by reference co-pending provisional application Serial No. 60/285,683 filed April 24, 2001.

FIELD OF THE INVENTION

[02] The invention relates to TIMP-1-binding human antibodies.

BACKGROUND OF THE INVENTION

[03] Tissue inhibitors of metalloproteases (TIMPs) inhibit metalloproteases, a family of endopeptide hydrolases. Metalloproteases are secreted by connective tissue and hematopoietic cells, use Zn^{2+} or Ca^{2+} for catalysis, and may be inactivated by metal chelators as well as TIMP molecules. Matrix metalloproteases (MMPs) participate in a variety of biologically important processes, including the degradation of many structural components of tissues, particularly the extracellular matrix (ECM).

[04] Degradation of extracellular matrix tissue is desirable in processes where destruction of existing tissues is necessary, *e.g.*, in embryo implantation (Reponen *et al.*, *Dev. Dyn. 202*, 388-96, 1995), embryogenesis, and tissue remodeling. Imbalance between synthesis and degradation of matrix proteins, however, can result in diseases such as liver fibrosis (Iredale *et al.*, *Hepatology 24*, 176-84, 1996). This imbalance can occur, for example, if levels of TIMPs are increased. Disorders in which TIMP-1 levels of increased include, for example, liver fibrosis, alcoholic liver disease, cardiac fibrosis, acute coronary syndrome, lupus nephritis, glomerulosclerotic renal disease, idiopathic pulmonary fibrosis, benign prostate hypertrophy, lung cancer, and colon cancer. *See, e.g.*, Inokubo

et al., Am. Heart J. 141, 211-17, 2001; Ylisirnio *et al., Anticancer Res. 20*, 1311-16, 2000; Holten-Andersen *et al., Clin. Cancer Res. 6*, 4292-99, 2000; Holten-Andersen *et al., Br. J. Cancer 80*, 495-503, 1999; Peterson *et al., Cardiovascular Res. 46*, 307-15, 2000; Arthur *et al., Alcoholism: Clinical and Experimental Res. 23*, 840-43, 1999; Iredale *et al., Hepatol. 24*, 176-84, 1996.

[06] There is a need in the art for reagents and methods of inhibiting TIMP-1 activity, which can be used to provide therapeutic effects.

BRIEF SUMMARY OF THE INVENTION

[07] It is an object of the present invention to provide reagents and methods of inhibiting TIMP-1 activity. This and other objects of the invention are provided by one or more of the embodiments described below.

[08] One embodiment of the invention is a purified preparation of a human antibody, wherein the antibody binds to a tissue inhibitor of metalloprotease-1 (TIMP-1) and neutralizes a matrix metalloprotease (MMP)-inhibiting activity of the TIMP-1.

[09] Another embodiment of the invention is a purified preparation of a first human antibody which comprises a VHCDR3 region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360.

[10] Still another embodiment of the invention is a purified preparation of a first human antibody which comprises a VLCDR3 region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379.

[11] Yet another embodiment of the invention is a purified preparation of a first human antibody which has TIMP-1 binding and MMP-inhibiting activity characteristics of a second human antibody. The second antibody comprises a VHCDR3 and VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NO:3 and 46, SEQ ID NOS:4 and 47, SEQ ID NOS:5

and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:8 and 51, SEQ ID NOS:9 and 52, SEQ ID NOS:10 and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ ID NOS:26 and 69, SEQ ID NOS: 27 and 70, SEQ ID NOS:28 and 71, SEQ ID NOS:29 and 72, SEQ ID NOS:30 and 73, SEQ ID NOS:31 and 74, SEQ ID NOS:32 and 75, SEQ ID NOS:33 and 76, SEQ ID NOS:34 and 77, SEQ ID NOS:35 and 78, SEQ ID NOS:36 and 79, SEQ ID NOS:37 and 80, SEQ ID NOS:38 and 81, SEQ ID NOS:39 and 82, SEQ ID NOS:40 and 83, SEQ ID NOS:41 and 84, SEQ ID NOS:42 and 85, SEQ ID NOS:43 and 86, SEQ ID NOS:3 and 48, SEQ ID NOS:360 and 48, SEQ ID NOS:3 and 365, SEQ ID NOS:16 and 59, SEQ ID NOS:18 and 61, SEQ ID NOS:34 and 77, SEQ ID NOS:34 and 379, SEQ ID NOS:18 and 376, SEQ ID NOS:18 and 377, and SEQ ID NOS:18 and 378.

[12] Even another embodiment of the invention is a purified preparation of a human antibody comprising a VHCDR3 and VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NO:3 and 46, SEQ ID NOS:4 and 47, SEQ ID NOS:5 and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:8 and 51, SEQ ID NOS:9 and 52, SEQ ID NOS:10 and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ

ID NOS:26 and 69, SEQ ID NOS: 27 and 70, SEQ ID NOS:28 and 71, SEQ ID NOS:29 and 72, SEQ ID NOS:30 and 73, SEQ ID NOS:31 and 74, SEQ ID NOS:32 and 75, SEQ ID NOS:33 and 76, SEQ ID NOS:34 and 77, SEQ ID NOS:35 and 78, SEQ ID NOS:36 and 79, SEQ ID NOS:37 and 80, SEQ ID NOS:38 and 81, SEQ ID NOS:39 and 82, SEQ ID NOS:40 and 83, SEQ ID NOS:41 and 84, SEQ ID NOS:42 and 85, SEQ ID NOS:43 and 86, SEQ ID NOS:3 and 48, SEQ ID NOS:360 and 48, SEQ ID NOS:3 and 365, SEQ ID NOS:16 and 59, SEQ ID NOS:18 and 61, SEQ ID NOS:34 and 77, SEQ ID NOS:34 and 379, SEQ ID NOS:18 and 376, SEQ ID NOS:18 and 377, and SEQ ID NOS:18 and 378.

[13] A further embodiment of the invention is a purified preparation of a human antibody which comprises a heavy chain and a light chain amino acid pair selected from the group consisting of SEQ ID NOS:140 and 97, SEQ ID NOS:141 and 98, SEQ ID NOS:142 and 99, SEQ ID NOS:143 and 100, SEQ ID NOS:144 and 101, SEQ ID NOS:145 and 102, SEQ ID NOS:146 and 103, SEQ ID NOS:142 and 97, SEQ ID NOS:142 and 98, SEQ ID NOS:142 and 100, SEQ ID NOS:142 and 101, SEQ ID NOS:142 and 102, SEQ ID NOS:142 and 103, SEQ ID NOS:146 and 97, SEQ ID NOS:146 and 98, SEQ ID NO:146 and 100, SEQ ID NOS:146 and 101, SEQ ID NOS:148 and 104, SEQ ID NOS:148 and 105, SEQ ID NOS:149 and 106, SEQ ID NOS:150 and 107, SEQ ID NOS:151 and 108, SEQ ID NOS:152 and 109, SEQ ID NOS:153 and 110, SEQ ID NOS:154 and 111, SEQ ID NOS:155 and 112, SEQ ID NOS:156 and 113, SEQ ID NOS:157 and 114, SEQ ID NOS:158 and 115, SEQ ID NOS:159 and 116, SEQ ID NOS:160 and 117, SEQ ID NOS:161 and 118, SEQ ID NOS:162 and 119, SEQ ID NOS:163 and 120, SEQ ID NOS:164 and 121, SEQ ID NOS:165 and 122, SEQ ID NOS:166 and 123, SEQ ID NOS:167 and 124, SEQ ID NOS:168 and 125, SEQ ID NOS:169 and 126, SEQ ID NOS:170 and 127, SEQ ID NOS:171 and 128, SEQ ID NOS:172 and 129, SEQ ID NOS:173 and 130, SEQ ID NOS:174 and 131, SEQ ID NOS:175 and 132, SEQ ID NOS:176 and 133, SEQ ID NOS:177 and 134, SEQ ID NOS:178 and 135, SEQ ID NOS:179 and 136, SEQ ID NOS:180 and 137, SEQ ID NOS:181 and 138, and SEQ ID NOS:182 and 139.

[14] Another embodiment of the invention is a pharmaceutical composition comprising a human antibody and a pharmaceutically acceptable carrier. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.

[15] Yet another embodiment of the invention is a purified polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.

[16] Even another embodiment of the invention is a purified polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.

[17] Still another embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.

[18] A further embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The VHCDR3 region is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:227-269.

[19] Another embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID

NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.

[20] Yet another embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The VLCDR3 region is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:184-226.

[21] Still another embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human antibody comprises a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:140-182.

[22] Even another embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human antibody comprises a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:140-182. The heavy chain is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:269-311.

[23] A further embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human antibody comprises a light chain

having an amino acid sequence selected from the group consisting of SEQ ID NOS:97-139.

[24] Another embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human antibody comprises a light chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:97-139. The light chain is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:312-354.

[25] Yet another embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360, wherein the human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.

[26] Yet another embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360, wherein the human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The VHCDR3 region is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:227-269.

[27] Still another embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.

[28] A further embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The VLCDR3 region is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:184-226.

[29] Another embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360, wherein the human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human antibody comprises a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:140-182.

[30] Still another embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360, wherein the human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human antibody comprises a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:140-182. The heavy chain is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:269-311.

[31] Yet another embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human

antibody comprises a light chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:97-139.

[32] Even another embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human antibody comprises a light chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:97-139. The light chain is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:312-354.

[33] A further embodiment of the invention is a method of making a human antibody. The host cell of claim 43 is cultured under conditions whereby the antibody is expressed. The human antibody is purified from the host cell culture.

[34] Another embodiment of the invention is a method of decreasing an MMP-inhibiting activity of a TIMP-1. The TIMP-1 is contacted with a human antibody that binds to the TIMP-1. The MMP-inhibiting activity of the TIMP-1 is decreased relative to MMP-inhibiting activity of the TIMP-1 in the absence of the antibody.

[35] Still another embodiment of the invention is a method of ameliorating symptoms of a disorder in which TIMP-1 is elevated. An effective amount of a human antibody which neutralizes an MMP-inhibiting activity of the TIMP-1 is administered to a patient having the disorder. Symptoms of the disorder are thereby ameliorated.

[36] A further embodiment of the invention is a method of detecting a TIMP-1 in a test preparation. The test preparation is contacted with a human antibody that specifically binds to the TIMP-1. The test preparation is assayed for the presence of an antibody-TIMP-1 complex.

[37] Even another embodiment of the invention is a method to aid in diagnosing a disorder in which a TIMP-1 level is elevated. A sample from a patient suspected of having the disorder is contacted with a human antibody that binds to TIMP-1. The sample is assayed for the presence of an antibody-TIMP-1 complex. Detection of an amount of the complex which is greater than an amount of the complex in a normal sample identifies the patient as likely to have the disorder.

[38] The invention thus provides human antibodies which bind to TIMP-1 and neutralize MMP-inhibiting activity of TIMP-1. These antibodies can be used, *inter alia*, in diagnostic and therapeutic methods.

BRIEF DESCRIPTION OF THE FIGURES

[39] FIG. 1. Protein sequences encoded by the HuCAL® V_H and V_L Fab master genes. Seven V_H and V_L sequences are aligned, and the approximate location of restriction endonuclease sites introduced into the corresponding DNA sequences are indicated. The numbering is according to VBASE except for the gap in Vl position 9. In VBASE the gap is set at position 10. See also Chothia *et al.* (1992) *J. Mol. Biol. 227*, 776-798, Tomlinson *et al.* (1995) *EMBO J. 14*, 4628-4638 and Williams *et al.* (1996) *J. Mol. Biol. 264*, 220-232).

[40] FIG. 2. Nucleotide sequences of the HuCAL® V_H and V_L Fab master genes.

[41] FIG. 3. Fab display vector pMORPH® 18 Fab 1.

[42] FIG. 4. Vector map of pMORPH® x9Fab1_FS.

[43] FIG. 5. Sequence comparison between human and rat TIMP-1. Sequence regions in bold were used for peptide synthesis. Residues that make stronger direct contacts with MMP-3 are italicized, and residues that make weaker direct contacts with MMP-3 are underlined (Gomis-Ruth *et al.*, 1997).

[44] FIG. 6. Activity of MS-BW-3 in human TIMP-1/ MMP-1 assay. Antibody Fab fragments were diluted in triplicate to the indicated concentrations in assay buffer containing 0.05% BSA. After addition of TIMP (final conc. 1.2 nM), MMP (final conc. 1.2 nM), and peptide substrate (final conc. 50 μM) and incubation for 1-3 h at 37°C fluorescence at Ex320 nm/Em 430 nm was measured. IC_{50} was calculated as outlined in material and methods section, using 100% MMP-1 activity (in absence of TIMP-1) and 27% MMP-1 activity (in absence of antibody) as reference values.

[45] FIG. 7. Activity of MS-BW-44 in human TIMP-1/ MMP-1 assay. Antibody Fab fragments were diluted in triplicate to the indicated concentrations in assay buffer containing 0.05% BSA. After addition of TIMP (final conc. 1.2 nM), MMP (final conc. 1.2 nM), and peptide substrate (final conc. 50 μM) and incubation for 1-3 h at 37°C fluorescence at Ex320 nm/Em 430 nm was measured. IC_{50} was calculated as outlined in material and methods section, using 100% MMP-1 activity (in absence of TIMP-1) and 25% MMP-1 activity (in absence of antibody) as reference values.

[46] FIG. 8. Activity of MS-BW-44, -44-2, 44-6 in human TIMP-1/ MMP-1 assay. Fab antibody fragments were diluted in triplicate to the indicated concentrations in assay buffer containing 0.05% BSA. After addition of TIMP (final conc. 0.4 nM), MMP (final conc. 0.4 nM) and peptide substrate (final conc. 50 μM) and incubation for 7 h at 37°C fluorescence at Ex320 nm/Em 430 nm was measured. IC_{50} was calculated as outlined in material and methods section, using 100% MMP-1 activity (in absence of TIMP-1) and 55% MMP-1 activity (in absence of antibody) as reference values.

[47] FIG. 9. Activity of MS-BW-44, -44-2-4, 44-6-1 in human TIMP-1/ MMP-1 assay. Antibody Fab fragments were diluted in triplicate to the indicated concentrations in assay buffer containing 0.05% BSA. After addition of TIMP (final conc. 0.4 nM), MMP (final conc. 0.4 nM), and peptide substrate (final conc. 50 μM) and incubation for 7 h at 37°C fluorescence at Ex320 nm/Em 430 nm was measured. IC_{50} was calculated as outlined in

material and methods section, using 100% MMP-1 activity (in absence of TIMP-1) and 50% MMP-1 activity (in absence of antibody) as reference values.

[48] FIG. 10. Binding of Fab fragments to human TIMP-1, -2, -3 and –4. TIMP-1, -2, -3, -4 proteins were immobilized on an ELISA plate, and binding of purified Fab fragments was measured by incubation with alkaline phosphatase conjugated anti-Fab antibody (Dianova) followed by development with Attophos substrate (Roche) and measurement at Ex405nm/Em535 nm.

[49] FIG. 11. Activity of MS-BW-14, -17, -54 in rat TIMP-1/MMP-13 assay. Antibody Fab fragments were diluted in triplicate to the indicated concentrations in assay buffer containing 0.05% BSA. After addition of TIMP (final conc. 1.2 nM), MMP (final conc. 1.2 nM), and peptide substrate (to final conc. 50 μM) and incubation for 1-3 h at 37°C fluorescence at Ex320 nm/Em 430 nm was measured. IC_{50} was calculated as outlined in material and methods section, using 100% MMP-13 (in absence of TIMP-1) activity and 20% MMP-13 activity (in absence of antibody) as reference values.

[50] FIG. 12. Activity of MS-BW-14 Fab and IgG_1 and MS-BW-3 IgG_1 in rat TIMP-1/ MMP-13 assay. Antibodies were diluted in triplicate to the indicated concentrations in assay buffer containing 0.05% BSA. After addition of TIMP (final conc. 1.2 nM), MMP (final conc. 1.2 nM) and peptide substrate (to final conc.50 μM) and incubation for 1-3 h at 37°C, fluorescence at Ex320 nm/Em 430 nm was measured. IC_{50} was calculated as outlined in material and methods section, using 100% MMP-13 activity (in absence of TIMP-1) and 30% MMP-13 activity (in absence of antibody) as reference values.

[51] FIG. 13. Activity of MS-BW-17-1 Fab and IgG_1 in rat TIMP-1/ MMP-13 assay. Fab antibody fragments were diluted in triplicate to the indicated concentrations in assay buffer containing 0.05% BSA. After addition of TIMP (final conc. 1.2 nM), MMP (final conc. 1.2 nM) and peptide substrate (to final conc.50 μM) and incubation for 1-3 h at 37°C fluorescence at Ex320 nm/Em 430 nm was measured. IC_{50} was calculated as

outlined in material and methods section, using 100% MMP-13 activity (in absence of TIMP-1) and 15% MMP-13 activity (in absence of antibody) as reference values.

[52] FIG. 14. Effect of the inhibitory effect of MS-BW-17-1 TIMP-1 antibody on bleomycin-induced lung fibrotic collagen.

[53] FIG. 15. Effect of anti-TIMP-1 antibody on fibrotic collagen as stained by Sirus Red in carbon tetrachloride-induced rat liver fibrosis model. Sirius Red-stained area as percent of total field in carbon tetrachloride-treated rats treated with PBS, control antibody, and MS-BW-14 anti-TIMP-1 antibody.

DETAILED DESCRIPTION OF THE INVENTION

[54] The invention provides human antibodies that bind to TIMP-1. These antibodies are useful for a variety of therapeutic and diagnostic purposes.

Characteristics of Human TIMP-1 Antibodies

[55] "Antibody" as used herein includes intact immunoglobulin molecules (*e.g.*, IgG_1, IgG_{2a}, IgG_{2b}, IgG_3, IgM, IgD, IgE, IgA), as well as fragments thereof, such as Fab, F(ab')2, scFv, and Fv, which are capable of specific binding to an epitope of a human and/or rat TIMP-1 protein. Antibodies that specifically bind to TIMP-1 provide a detection signal at least 5-, 10-, or 20-fold higher than a detection signal provided with other proteins when used in an immunochemical assay. Preferably, antibodies that specifically bind to human and/or rat TIMP-1 do not detect other proteins in immunochemical assays and can immunoprecipitate the TIMP-1 from solution.

[56] The K_d of human antibody binding to TIMP-1 can be assayed using any method known in the art, including technologies such as real-time Bimolecular Interaction Analysis (BIA) (Sjolander & Urbaniczky, *Anal. Chem. 63*, 2338-45, 1991, and Szabo *et al.*, *Curr. Opin. Struct. Biol. 5*, 699-705, 1995). BIA is a technology for studying biospecific interactions in real time, without labeling any of the interactants (*e.g.*, BIAcore™).

Changes in the optical phenomenon surface plasmon resonance (SPR) can be used as an indication of real-time reactions between biological molecules.

[57] In a BIAcore™ assay, some human antibodies of the invention specifically bind to human TIMP-1 with a K_d of about 0.1 nM to about 10 μM, about 2 nM to about 1 μM, about 2 nM to about 200 nM, about 2 nM to about 150 nM, about 50 nM to about 100 nM, about 0.2 nM to about 13 nM, about 0.2 nM to about 0.5 nM, about 2 nM to about 13 nM, and about 0.5 nM to about 2 nM. More preferred human antibodies specifically bind to human TIMP-1 with a K_d selected from the group consisting of about 0.2 nM, about 0.3 nM, about 0.5 M, about 0.6 nM, about 2 nM, about 7 nM, about 10 nM, about 11 nM, and about 13 nM.

[58] Other human antibodies of the invention specifically bind to rat TIMP-1 with a K_d of about 0.1 nM to about 10 μM, about 2 nM to about 1 μM, about 2 nM to about 200 nM, about 2 nM to about 150 nM, about 50 nM to about 100 nM, about 1.3 nM to about 13 nM, about 1.8 nM to about 10 nM, about 2 nM to about 9 nM, about 1.3 nM to about 9 nM, and about 2 nM to about 10 nM. Preferred K_d s range from about 0.8 nM, about 1 nM, about 1.3 nM, about 1.9 nM, about 2 nM, about 3 nM, about 9 nM, about 10 nM, about 13 nM, about 14 nM, and about 15 nM.

[59] Preferably, antibodies of the invention neutralize an MMP-inhibiting activity of the TIMP-1. The MMP can be, for example, MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-10, MMP-11, MMP-12, MMP-13, MMP-19, MMP-20 or MMP-23.

[60] IC_{50} for neutralizing MMP-inhibiting activity of TIMP-1 can be measured by any means known in the art. Preferably, IC_{50} is determined using the high throughput fluorogenic assay described in Bickett *et al., Anal. Biochem. 212*, 58-64, 1993. In a typical fluorogenic assay, the IC_{50} of a human antibody for neutralizing human TIMP-1 MMP-inhibiting activity ranges from about .1 nM to about 200 nM, about 1 nM to about 100 nM, about 2 nM to about 50 nM, about 5 nM to about 25 nM, about 10 nM to about 15 nM, about 0.2 nM to about 11 nM, about 0.2 nM to about 4 nM, and about 4 nM to about

11 nM. The IC_{50} for neutralizing human TIMP-1 MMP-inhibiting activity of some human antibodies is about 0.2 nM, about 0.3 nM, about 0.4 nM, about 4 nM, about 7 nM, about 9 nM, and about 11 nM.

[61] A typical IC_{50} for neutralizing rat TIMP-1 MMP-inhibiting activity ranges from about .1 nM to about 300 nM, about 1 nM to about 100 nM, about 2 nM to about 50 nM, about 5 nM to about 25 nM, about 10 nM to about 15 nM, about 1.1 nM to about 14 nM, about 1.6 nM to about 11 nM, about 3 nM to about 7 nM, about 1.1 nM to about 7 nM, about 1.1 nM to about 11 nM, about 3 nM to about 11 nM, and about 3 nM to about 14 nM. The IC_{50} for neutralizing rat TIMP-1 MMP-inhibiting activity of some human antibodies is about 1.1 nM, about 1.6 nM, about 3 nM, about 7 nM, about 11 nM, about 14 nM, about 19 nM, about 20 nM, about 30 nM, and about 100 nM.

[62] Preferred human antibodies of the invention are those for which the K_d for binding to TIMP-1 and the IC_{50} for neutralizing the MMP-inhibiting activity of the TIMP-1 are approximately equal.

[63] A number of human antibodies having the TIMP-1 binding and MMP-inhibiting activity neutralizing characteristics described above have been identified by screening the MorphoSys HuCAL® Fab 1 library. The CDR cassettes assembled for the HuCAL® library were designed to achieve a length distribution ranging from 5 to 28 amino acid residues, covering the stretch from position 95 to 102. Knappik *et al.*, *J. Mol. Biol. 296*, 57-86, 2000. Some clones, however, had shorter VHCDR3 regions. In fact, it is a striking feature of anti-human TIMP-1 human antibodies identified from this library that they all exhibit the combination VH3l2 and a relatively short VHCDR3 region, typically four amino acids.

[64] In some embodiments of the invention, the VHCDR3 region of a human antibody has an amino acid sequence shown in SEQ ID NOS:1-43. In other embodiments of the invention, the VLCDR3 region of a human antibody has an amino acid sequence shown in SEQ ID NOS:44-86. See Tables 2, 3, and 7. Human antibodies which have TIMP-1

binding and MMP-inhibiting activity neutralizing characteristics of antibodies such as those described above and in Tables 2, 3, and 7 also are human antibodies of the invention.

Obtaining human antibodies

[65] Human antibodies with the TIMP-1 binding and MMP-activity neutralizing characteristics described above can be identified from the MorphoSys HuCAL® library as follows. Human or rat TIMP-1, for example, is coated on a microtiter plate and incubated with the MorphoSys HuCAL® Fab phage library (see Example 1, below). Those phage-linked Fabs not binding to TIMP-1 can be washed away from the plate, leaving only phage which tightly bind to TIMP-1. The bound phage can be eluted, for example, by a change in pH or by elution with *E. coli* and amplified by infection of *E. coli* hosts. This panning process can be repeated once or twice to enrich for a population of antibodies that tightly bind to TIMP-1. The Fabs from the enriched pool are then expressed, purified, and screened in an ELISA assay. The identified hits are then screened in the enzymatic assay described in Bickett *et al.*, 1993, and Bodden *et al.*, 1994. Those Fabs that lead to the degradation of the peptide are likely the ones which bind to TIMP-1, thereby blocking its interaction to MMP-1.

[66] The initial panning of the HuCAL® Fab 1 library also can be performed with TIMP-1 as the antigen in round one, followed in round 2 by TIMP-1 peptides fused to carrier proteins, such as BSA or transferrin, and in round 3 by TIMP-1 again. Human TIMP-1 peptides which can be used for panning include human TIMP-1 residues 2-12 (TCVPPHPQTAF, SEQ ID NO:87; CTSVPPHPQTAF, SEQ ID NO:88; STCVPPHPQTAF, SEQ ID NO:89; STSVPPHPQTAFC, SEQ ID NO:90), 28-36 (CEVNQTTLYQ, SEQ ID NO:91), 64-75 (PAMESVCGYFHR, SEQ ID NO:92), 64-79 (PAMESVCGYFHRSHNR, SEQ ID NO:93; CPAMESVSGYFHRSHNR, SEQ ID NO:94; PAMESVSGYFHRSHNRC, SEQ ID NO:95), and 145-157 (CLWTDQLLQGSE, SEQ ID NO:96). These peptide sequences are selected from

regions of human TIMP-1 that are predicted to interact with MMPs. See Gomis-Ruth *et al.*, *Nature 389*, 77-81, 1997. Directing Fabs toward the MMP-interacting region of human TIMP-1 in round 2 should increase the chance of identifying Fabs that can block the ability of human TIMP-1 to inhibit human MMP-1 activity.

[67] Another method that can be used to improve the likelihood of isolating neutralizing Fabs is the panning on human TIMP-1 and eluting the binding Fabs with human MMP-1. This strategy should yield higher affinity antibodies than would otherwise be obtained.

[68] Details of the screening process are described in the specific examples, below. Other selection methods for highly active specific antibodies or antibody fragments can be envisioned by those skilled in the art and used to identify human TIMP-1 antibodies.

[69] Human antibodies with the characteristics described above also can be purified from any cell that expresses the antibodies, including host cells that have been transfected with antibody-encoding expression constructs. The host cells are cultured under conditions whereby the human antibodies are expressed. A purified human antibody is separated from other compounds that normally associate with the antibody in the cell, such as certain proteins, carbohydrates, or lipids, using methods well known in the art. Such methods include, but are not limited to, size exclusion chromatography, ammonium sulfate fractionation, ion exchange chromatography, affinity chromatography, and preparative gel electrophoresis. A preparation of purified human antibodies is at least 80% pure; preferably, the preparations are 90%, 95%, or 99% pure. Purity of the preparations can be assessed by any means known in the art, such as SDS-polyacrylamide gel electrophoresis. A preparation of purified human antibodies of the invention can contain more than one type of human antibody with the TIMP-1 binding and neutralizing characteristics described above.

[70] Alternatively, human antibodies can be produced using chemical methods to synthesize its amino acid sequence, such as by direct peptide synthesis using solid-phase techniques (Merrifield, *J. Am. Chem. Soc. 85*, 2149-54, 1963; Roberge *et al.*, *Science 269*, 202-04,

1995). Protein synthesis can be performed using manual techniques or by automation. Automated synthesis can be achieved, for example, using Applied Biosystems 431A Peptide Synthesizer (Perkin Elmer). Optionally, fragments of human antibodies can be separately synthesized and combined using chemical methods to produce a full-length molecule.

[71] The newly synthesized molecules can be substantially purified by preparative high performance liquid chromatography (*e.g.*, Creighton, PROTEINS: STRUCTURES AND MOLECULAR PRINCIPLES, WH Freeman and Co., New York, N.Y., 1983). The composition of a synthetic polypeptide can be confirmed by amino acid analysis or sequencing (*e.g.*, using Edman degradation).

Assessment of therapeutic utility of human antibodies

[72] To assess the ability of a particular antibody to be therapeutically useful to treat, liver fibrosis, for example, the antibody can be tested *in vivo* in a rat liver fibrosis model. Thus, preferred human antibodies of the invention are able to block both human and rat TIMP-1 activity. If desired, human Fab TIMP-1 antibodies can be converted into full immunoglobulins, for example IgG_1 antibodies, before therapeutic assessment. This conversion is described in Example 5, below.

[73] To identify antibodies that cross-react with human and rat TIMP-1, an ELISA can be carried out using rat TIMP-1. Functional cross-reactivity can be confirmed in an enzymatic assay, as described in Bickett *et al.*, *Anal. Biochem. 212*, 58-64, 1993. The assay uses human or rat TIMP-1, human MMP-1 or rat MMP-13 (the rat counterpart of human MMP-1), and a synthetic fluorogenic peptide substrate. Enzyme activity of uncomplexed MMP-1 (or MMP-13) is assessed by observing an increase in a fluorescence signal.

[74] Antibodies that block human and/or rat TIMP-1 activity can be screened in an ELISA assay that detects the decrease of TIMP-1/MMP-1 complex formation in cultures of

HepG2 cells. Antibodies that meet this criteria can then be tested in a rat liver fibrosis model to assess therapeutic efficacy and correlate this efficacy with the ability of the antibodies to block TIMP-1 inhibition of MMP-1 *in vitro*.

[75] Antibodies that demonstrate therapeutic efficacy in the rat liver fibrosis model can then be tested for binding to and blockade of TIMP-2, -3, and -4 in an *in vitro* enzymatic assay. Blocking the minimum number of TIMPs necessary for efficacy in liver fibrosis or other TIMP-associated pathology is preferable to minimize potential side effects.

Polynucleotides encoding human TIMP-1 antibodies

[76] The invention also provides polynucleotides encoding human TIMP-1 antibodies. These polynucleotides can be used, for example, to produce quantities of the antibodies for therapeutic or diagnostic use.

[77] Polynucleotides that can be used to encode the VHCDR3 regions shown in SEQ ID NOS:1-43 are shown in SEQ ID NOS:226-268, respectively. Polynucleotides that can be used to encode the VLCDR3 region shown in SEQ ID NOS:44-86 are shown in SEQ ID NOS:183-225, respectively. Polynucleotides that encode heavy chains (SEQ ID NOS:140-182) and light chains (SEQ ID NOS:97-139) of human antibodies of the invention that have been isolated from the MorphoSys HuCAL® library are shown in SEQ ID NOS:269-311 and SEQ ID NOS:312-354, respectively.

[78] Polynucleotides of the invention present in a host cell can be isolated free of other cellular components such as membrane components, proteins, and lipids. Polynucleotides can be made by a cell and isolated using standard nucleic acid purification techniques, or synthesized using an amplification technique, such as the polymerase chain reaction (PCR), or by using an automatic synthesizer. Methods for isolating polynucleotides are routine and are known in the art. Any such technique for obtaining a polynucleotide can be used to obtain isolated polynucleotides encoding antibodies of the invention. For example, restriction enzymes and probes can be used to

isolate polynucleotides which encode the antibodies. Isolated polynucleotides are in preparations that are free or at least 70, 80, or 90% free of other molecules.

[79] Human antibody-encoding DNA molecules of the invention can be made with standard molecular biology techniques, using mRNA as a template. Thereafter, DNA molecules can be replicated using molecular biology techniques known in the art and disclosed in manuals such as Sambrook *et al.* (1989). An amplification technique, such as PCR, can be used to obtain additional copies of the polynucleotides.

[80] Alternatively, synthetic chemistry techniques can be used to synthesize polynucleotides encoding antibodies of the invention. The degeneracy of the genetic code allows alternate nucleotide sequences to be synthesized that will encode an antibody having, for example, one of the VHCDR3, VLCDR3, light chain, or heavy chain amino acid sequences shown in SEQ ID NOS:1-43, 44-86, 97-139, or 140-182, respectively.

Expression of polynucleotides

[81] To express a polynucleotide encoding a human antibody of the invention, the polynucleotide can be inserted into an expression vector that contains the necessary elements for the transcription and translation of the inserted coding sequence. Methods that are well known to those skilled in the art can be used to construct expression vectors containing sequences encoding human antibodies and appropriate transcriptional and translational control elements. These methods include *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. Such techniques are described, for example, in Sambrook *et al.* (1989) and in Ausubel *et al.*, CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, New York, N.Y., 1995. See also Examples 1-3, below.

[82] A variety of expression vector/host systems can be utilized to contain and express sequences encoding a human antibody of the invention. These include, but are not limited to, microorganisms, such as bacteria transformed with recombinant

bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors, insect cell systems infected with virus expression vectors (*e.g.*, baculovirus), plant cell systems transformed with virus expression vectors (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or with bacterial expression vectors (*e.g.*, Ti or pBR322 plasmids), or animal cell systems.

[83] The control elements or regulatory sequences are those non-translated regions of the vector -- enhancers, promoters, 5' and 3' untranslated regions -- which interact with host cellular proteins to carry out transcription and translation. Such elements can vary in their strength and specificity. Depending on the vector system and host utilized, any number of suitable transcription and translation elements, including constitutive and inducible promoters, can be used. For example, when cloning in bacterial systems, inducible promoters such as the hybrid lacZ promoter of the BLUESCRIPT phagemid (Stratagene, LaJolla, Calif.) or pSPORT1 plasmid (Life Technologies) and the like can be used. The baculovirus polyhedrin promoter can be used in insect cells. Promoters or enhancers derived from the genomes of plant cells (*e.g.*, heat shock, RUBISCO, and storage protein genes) or from plant viruses (*e.g.*, viral promoters or leader sequences) can be cloned into the vector. In mammalian cell systems, promoters from mammalian genes or from mammalian viruses are preferable. If it is necessary to generate a cell line that contains multiple copies of a nucleotide sequence encoding a human antibody, vectors based on SV40 or EBV can be used with an appropriate selectable marker.

[84] Large scale production of human TIMP-1 antibodies can be carried out using methods such as those described in Wurm *et al., Ann. N.Y. Acad. Sci. 782*, 70-78, 1996, and Kim *et al., Biotechnol. Bioengineer. 58*, 73-84, 1998.

Pharmaceutical compositions

[85] Any of the human TIMP-1 antibodies described above can be provided in a pharmaceutical composition comprising a pharmaceutically acceptable carrier. The pharmaceutically acceptable carrier preferably is non-pyrogenic. The compositions can

be administered alone or in combination with at least one other agent, such as stabilizing compound, which can be administered in any sterile, biocompatible pharmaceutical carrier, including, but not limited to, saline, buffered saline, dextrose, and water. A variety of aqueous carriers may be employed, *e.g.*, 0.4% saline, 0.3% glycine, and the like. These solutions are sterile and generally free of particulate matter. These solutions may be sterilized by conventional, well known sterilization techniques (*e.g.*, filtration). The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions such as pH adjusting and buffering agents, etc. The concentration of the antibody of the invention in such pharmaceutical formulation can vary widely, *i.e.*, from less than about 0.5%, usually at or at least about 1% to as much as 15 or 20% by weight and will be selected primarily based on fluid volumes, viscosities, etc., according to the particular mode of administration selected. See U.S. Patent 5,851,525. If desired, more than one type of human antibody, for example with different K_d for TIMP-1 binding or with different IC_{50}s for MMP-inhibiting activity neutralization, can be included in a pharmaceutical composition.

[86] The compositions can be administered to a patient alone, or in combination with other agents, drugs or hormones. In addition to the active ingredients, these pharmaceutical compositions can contain suitable pharmaceutically-acceptable carriers comprising excipients and auxiliaries that facilitate processing of the active compounds into preparations which can be used pharmaceutically. Pharmaceutical compositions of the invention can be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal, parenteral, topical, sublingual, or rectal means.

[87] After pharmaceutical compositions have been prepared, they can be placed in an appropriate container and labeled for treatment of an indicated condition. Such labeling would include amount, frequency, and method of administration.

Methods of decreasing MMP-inhibiting activity of human TIMP-1

[88] The invention provides methods of decreasing an MMP-inhibiting activity of human or rat TIMP-1. Such methods can be used therapeutically, as described below, or in a research setting. Thus, the methods can be carried out in a cell-free system, in a cell culture system, or *in vivo*. *In vivo* methods of decreasing MMP-inhibiting activity of human or rat TIMP-1 are described below.

[89] Human TIMP-1 is contacted with a human antibody that binds to the human TIMP-1, thereby decreasing the MMP-inhibiting activity of the human TIMP-1 relative to human TIMP-1 activity in the absence of the antibody. The antibody can be added directly to the cell-free system, cell culture system, or to an animal subject or patient, or can be provided by means of an expression vector encoding the antibody.

Diagnostic methods

[90] The invention also provides diagnostic methods, with which human or rat TIMP-1 can be detected in a test preparation, including without limitation a sample of serum, lung, liver, heart, kidney, colon, a cell culture system, or a cell-free system (*e.g.*, a tissue homogenate). Such diagnostic methods can be used, for example, to diagnose disorders in which TIMP-1 is elevated. Such disorders include, but are not limited to, liver fibrosis, alcoholic liver disease, cardiac fibrosis, acute cardiac syndrome, lupus nephritis, glomerulosclerotic renal disease, benign prostate hypertrophy, lung cancer, colon cancer, and idiopathic pulmonary fibrosis. When used for diagnosis, detection of an amount of the antibody-TIMP-1 complex in a test sample from a patient which is greater than an amount of the complex in a normal sample identifies the patient as likely to have the disorder.

[91] The test preparation is contacted with a human antibody of the invention, and the test preparation is then assayed for the presence of an antibody-TIMP-1 complex. If desired, the human antibody can comprise a detectable label, such as a fluorescent, radioisotopic,

chemiluminescent, or enzymatic label, such as horseradish peroxidase, alkaline phosphatase, or luciferase.

[92] Optionally, the antibody can be bound to a solid support, which can accommodate automation of the assay. Suitable solid supports include, but are not limited to, glass or plastic slides, tissue culture plates, microtiter wells, tubes, silicon chips, or particles such as beads (including, but not limited to, latex, polystyrene, or glass beads). Any method known in the art can be used to attach the antibody to the solid support, including use of covalent and non-covalent linkages, passive absorption, or pairs of binding moieties attached to the antibody and the solid support. Binding of TIMP-1 and the antibody can be accomplished in any vessel suitable for containing the reactants. Examples of such vessels include microtiter plates, test tubes, and microcentrifuge tubes.

Therapeutic methods

[93] The invention also provides methods of ameliorating symptoms of a disorder in which TIMP-1 is elevated. These disorders include, without limitation, liver fibrosis alcoholic liver disease, cardiac fibrosis, acute coronary syndrome, lupus nephritis, glomerulosclerotic renal disease, idiopathic pulmonary fibrosis, benign prostate hypertrophy, lung cancer, colon cancer, and scarring. *See, e.g.*, Inokubo *et al.*, *Am. Heart J. 141*, 211-17, 2001; Ylisirnio *et al.*, *Anticancer Res. 20*, 1311-16, 2000; Holten-Andersen *et al.*, *Clin. Cancer Res. 6*, 4292-99, 2000; Holten-Andersen *et al.*, *Br. J. Cancer 80*, 495-503, 1999; Peterson *et al.*, *Cardiovascular Res. 46*, 307-15, 2000; Arthur *et al.*, *Alcoholism: Clinical and Experimental Res. 23*, 840-43, 1999; Iredale *et al.*, *Hepatol. 24*, 176-84, 1996.

[94] Human antibodies of the invention are particularly useful for treating liver fibrosis. All chronic liver diseases cause the development of fibrosis in the liver. Fibrosis is a programmed uniform wound healing response. Toxic damage or injury caused by foreign proteins cause the deposition of extracellular matrix such as collagen, fibronectin, and laminin. Liver fibrosis and cirrhosis can be caused by chronic degenerative diseases

of the liver such as viral hepatitis, alcohol hepatitis, autoimmune hepatitis, primary biliary cirrhosis, cystic fibrosis, hemochromatosis, Wilson's disease, and non-alcoholic steato-hepatitis, as well as chemical damage.

[95] Altered degradation and synthesis of extracellular matrix (particularly collagens) play central roles in pathogenesis of liver fibrosis. In the early phases, hepatic stellate cells (HSC) are initially activated and release matrix metalloproteases with the ability to degrade the normal liver matrix. When HSC are fully activated, there is a net down-regulation of matrix degradation mediated by increased synthesis and extracellular release of tissue inhibitors of metalloprotease (TIMP)-1 and -2. The dynamic regulation of activity of metalloproteases during liver fibrosis makes them and their inhibitors targets for therapeutic intervention.

[96] Human antibodies of the invention are also particularly useful for treating lung fibrosis. Lung airway fibrosis is a hallmark of airway remodeling in patients with chronic asthma, so human antibodies of the invention are also particularly useful for chronic asthma. Airway remodeling is a well-recognized feature in patients with chronic asthma. TIMP-1 but not TIMP-2 levels were significantly higher in untreated asthmatic subjects than in glucocorticoid-treated subjects or controls ($p < 0.0001$), and were far greater than those of MMP-1, MMP-2, MMP-3, and MMP-9 combined (Mautino *et al.*, Am J Respir Crit Care Med 1999 160:324-330). TIMP-1 mRNA and protein expression are selectively and markedly increased in a murine model of bleomycin-induced pulmonary fibrosis (Am. J. Respir. Cell Mol. Biol. 24:599-607, 2001). This specific elevation of TIMP-1 without increase in MMPs in asthma patients suggests that inhibition of TIMP-1 by an antibody can restore normal collagen degradation in the lung.

[97] Human antibodies of the invention are also particularly useful for treating cancer. TIMP-1 protein has been found to be elevated in plasma of colon (Holten-Andersen et al., Br J Cancer 1999, 80:495-503) and prostate (Jung et al., Int J Cancer, 1997, 74:220-223) cancer patients, and high TIMP-1 plasma level correlates with poor clinical outcome of

colon cancer (Holten-Andersen et al., Clin Cancer Res 2000 6:4292-4299). TIMP-1 induces dose-dependent proliferation of breast tumorigenic clonal cell line and tyrosine phosphorylation (Luparello et al, Breast Cancer Res Treat, 1999, 54:235-244). Therefore, the use of antibody against TIMP-1 may block its ability to induce cancer.

[98] Human TIMP-1 antibodies can be used to prevent or diminish scar formation, such as scar formation after surgery (particularly ophthalmic surgery) or injury (such as a burn, scrape, crush, cut or tear injury).

[99] In one embodiment of the invention, a therapeutically effective dose of a human antibody of the invention is administered to a patient having a disorder in which TIMP-1 is elevated, such as those disorders described above. Symptoms of the disorder, including deposition of extracellular matrix, as well as loss of tissue or organ function, are thereby ameliorated.

Determination of a Therapeutically Effective Dose

[100] The determination of a therapeutically effective dose is well within the capability of those skilled in the art. A therapeutically effective dose refers to that amount of human antibody that reduces MMP-inhibiting activity of the TIMP-1 relative to the activity which occurs in the absence of the therapeutically effective dose.

[101] The therapeutically effective dose can be estimated initially either in cell culture assays or in animal models, usually rats, mice, rabbits, dogs, or pigs. The animal model also can be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans. A rat liver fibrosis model is described in Example 6.

[102] Therapeutic efficacy and toxicity, *e.g.*, ED_{50} (the dose therapeutically effective in 50% of the population) and LD_{50} (the dose lethal to 50% of the population) of a human antibody, can be determined by standard pharmaceutical procedures in cell cultures or experimental

animals. The dose ratio of toxic to therapeutic effects is the therapeutic index, and it can be expressed as the ratio, LD_{50}/ED_{50}.

[103] Pharmaceutical compositions that exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies is used in formulating a range of dosage for human use. The dosage contained in such compositions is preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, sensitivity of the patient, and the route of administration.

[104] The exact dosage will be determined by the practitioner, in light of factors related to the patient who requires treatment. Dosage and administration are adjusted to provide sufficient levels of the human antibody or to maintain the desired effect. Factors that can be taken into account include the severity of the disease state, general health of the subject, age, weight, and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. Long-acting pharmaceutical compositions can be administered every 3 to 4 days, every week, or once every two weeks depending on the half-life and clearance rate of the particular formulation.

[105] Polynucleotides encoding human antibodies of the invention can be constructed and introduced into a cell either *ex vivo* or *in vivo* using well-established techniques including, but not limited to, transferrin-polycation-mediated DNA transfer, transfection with naked or encapsulated nucleic acids, liposome-mediated cellular fusion, intracellular transportation of DNA-coated latex beads, protoplast fusion, viral infection, electroporation, "gene gun," and DEAE- or calcium phosphate-mediated transfection.

[106] Effective *in vivo* dosages of an antibody are in the range of about 5 mg to about 50 mg/kg, about 50 mg to about 5 mg/kg, about 100 mg to about 500 mg/kg of patient body weight, and about 200 to about 250 mg/kg of patient body weight. For administration of polynucleotides encoding the antibodies, effective *in vivo* dosages are in the range of

about 100 ng to about 200 ng, 500 ng to about 50 mg, about 1 mg to about 2 mg, about 5 mg to about 500 mg, and about 20 mg to about 100 mg of DNA.

[107] The mode of administration of human antibody-containing pharmaceutical compositions of the invention can be any suitable route which delivers the antibody to the host. Pharmaceutical compositions of the invention are particularly useful for parenteral administration, *i.e.*, subcutaneous, intramuscular, intravenous, or intranasal administration.

[108] All patents, patent applications, and references cited in this disclosure are expressly incorporated herein by reference. The above disclosure generally describes the present invention. A more complete understanding can be obtained by reference to the following specific examples, which are provided for purposes of illustration only and are not intended to limit the scope of the invention.

EXAMPLE 1

Construction of a Human Combinatorial Antibody Library (HuCAL® Fab 1)

[109] *Cloning of HuCAL® Fab 1.* HuCAL® Fab 1 is a fully synthetic, modular human antibody library in the Fab antibody fragment format. HuCAL® Fab 1 was assembled starting from an antibody library in the single-chain format (HuCAL® -scFv; Knappik *et al.*, *J. Mol. Biol. 296*, 55, 2000). HuCAL® Fab 1 was cloned into a phagemid expression vector pMORPH® 18 Fab1 (FIG. 3). This vector comprises the Fd fragment with a phoA signal sequence fused at the C-terminus to a truncated gene III protein of filamentous phage, and further comprises the light chain VL-CL with an ompA signal sequence. Both chains are under the control of the lac operon. The constant domains C?, C?, and CH are synthetic genes fully compatible with the modular system of HuCAL® (Knappik *et al.*, 2000).

[110] First, the V? and V? libraries were isolated from HuCAL®-scFv. V?1 fragments were amplified by 15 PCR cycles (Pwo polymerase) with primers 5'-

GTGGTGGTTCCGATATC-3′ (SEQ ID NO:380) and 5′- AGCGTCACA-CTCGGTGCGGCTTTCGGCTGGCCAAGAACGGTTA-3′ (SEQ ID NO:381). PCR-products were digested with EcoRV / DraIII and gel-purified. VL?-chains were obtained by restriction digest with EcoRV / BsiWI and gel-purified. These V? and V? libraries were cloned into pMORPH® 18 Fab1 cut with *Eco*RV / *Dra*III and *Eco*RV / *Bsi*WI, respectively. After ligation and transformation in *E. coli* TG-1, library sizes of 4.14 x 10^8 and 1.6 x 10^8, respectively, were obtained, in both cases exceeding the V? diversity of HuCAL®-scFv.

[111] Similarly, the VH library was isolated from HuCAL®-scFv by restriction digest using *Sty*I / *Mun*I. This VH library was cloned into the pMORPH® 18-V? and V? libraries cut with *Sty*I / *Mun*I. After ligation and transformation in *E. coli* TG-1, a total library size of 2.09 x 10^{10} was obtained, with 67% correct clones (as identified by sequencing of 207 clones).

[112] *Phagemid rescue, phage amplification and purification.* HuCAL® Fab was amplified in 2 x TY medium containing 34 µg/ml chloramphenicol and 1 % glucose (2 x TY-CG). After helper phage infection (VCSM13) at 37°C at an OD_{600} of about 0.5, centrifugation and resuspension in 2 x TY / 34 µg/ml chloramphenicol/ 50 µg/ml kanamycin, cells were grown overnight at 30°C. Phage were PEG-precipitated from the supernatant (Ausubel *et al.*, 1998), resuspended in PBS/20% glycerol, and stored at –80°C. Phage amplification between two panning rounds was conducted as follows: mid-log phase TG1-cells were infected with eluted phage and plated onto LB-agar supplemented with 1% of glucose and 34 µg/ml of chloramphenicol. After overnight incubation at 30°C, colonies were scraped off and adjusted to an OD_{600} of 0.5. Helper phage were added as described above.

EXAMPLE 2

Solid phase panning

[113] Wells of MaxiSorp™ microtiter plates (Nunc) were coated with rat- or human TIMP protein diluted to 50 μg/ml dissolved in PBS (2 μg/well). After blocking with 5% non-fat dried milk in PBS, 1–5 x 10^{12} HuCAL® Fab phage purified as above were added for 1h at 20°C. After several washing steps, bound phage were eluted by pH-elution with 100 mM triethylamine and subsequent neutralization with 1M TRIS-Cl pH 7.0. See Krebs *et al.*, *J. Immunol. Meth. 254*, 67, 2001. Two to three rounds of panning were performed with phage amplification conducted between each round as described above.

EXAMPLE 3

Solution panning

[114] Biotinylated antigen was diluted to 40 nM in PBS, 1013 HuCAL®-Fab 1 phage were added and incubated for 1 h at 20°C. Phage-antigen complexes were captured on Neutravidin plates (Pierce). After several washing steps, bound phages were eluted by different methods (Krebs *et al.*, 2001). Two rounds of panning were routinely performed.

EXAMPLE 4

Subcloning of selected Fab fragments for expression

[115] The Fab-encoding inserts of the selected HuCAL® Fab 1 fragments were subcloned into the expression vector pMORPH® x7_FS (Knappik *et al.*, *J. Mol. Biol. 296*, 55, 2000) to facilitate rapid expression of soluble Fab. The DNA preparation of the selected HuCAL® Fab 1 clones was digested with *Xba*I / *Eco*RI, thus cutting out the Fab encoding insert (ompA-VL and phoA-Fd). Subcloning of the purified inserts into the *Xba*I / *Eco*RI cut vector pMORPH® x7, previously carrying a scFv insert, produces a Fab expression vector designated pMORPH® x9_Fab1_FS (FIG. 4). Fabs expressed in this vector carry two C-terminal tags (FLAG™ and Strep-tagII) for detection and purification.

EXAMPLE 5

Identification of TIMP-binding Fab fragments by ELISA

[116] The wells of 384-well Maxisorp ELISA plates were coated with 20 µl/well solutions of rat TIMP or human TIMP at a concentration of 5 µg/ml diluted in coating buffer. Expression of individual Fab in *E. coli* TG-1 from expression vector pMORPH® x9_FS was induced with 0.5 mM IPTG for 12 h at 30°C. Soluble Fab was extracted from the periplasm by osmotic shock (Ausubel *et al.*, 1998) and used in an ELISA. The Fab fragment was detected after incubation with alkaline phosphatase-conjugated anti-Fab antibody (Dianova), followed by development with Attophos substrate (Roche) and measurement at Ex450 nm / Em535 nm. Values at 370 nm were read out after addition of horseradish peroxidase-conjugated anti-mouse IgG antibody and POD soluble substrate (Roche Diagnostics).

EXAMPLE 6

Expression and purification of HuCAL®-Fab 1 antibodies in E. coli

[117] Expression of Fab fragments encoded by pMORPH® x9_FS in TG-1 cells was carried out in shaker flask cultures with 1 liter of 2xTY medium supplemented with 34 µg/ml chloramphenicol. After induction with 0.5 mM IPTG, cells were grown at 22°C for 16 h. Periplasmic extracts of cell pellets were prepared, and Fab fragments were isolated by Strep-tactin® chromatography (IBA, Goettingen, Germany). The apparent molecular weights were determined by size exclusion chromatography (SEC) with calibration standards. Concentrations were determined by UV-spectrophotometry.

EXAMPLE 7

Construction of HuCAL® immunoglobulin expression vectors

[118] *Heavy chain cloning.* The multiple cloning site of pcDNA3.1+ (Invitrogen) was removed (*Nhe*I / *Apa*I), and a stuffer compatible with the restriction sites used for HuCAL® design

was inserted for the ligation of the leader sequences (*Nhe*I / *Eco*RI), VH-domains (*Eco*RI / *Blp*I), and the immunoglobulin constant regions (*Blp*I / *Apa*I). The leader sequence (EMBL M83133) was equipped with a Kozak sequence (Kozak, 1987). The constant regions of human IgG_1 (PIR J00228), IgG_4 (EMBL K01316), and serum IgA_1 (EMBL J00220) were dissected into overlapping oligonucleotides with lengths of about 70 bases. Silent mutations were introduced to remove restriction sites non-compatible with the HuCAL® design. The oligonucleotides were spliced by overlap extension-PCR.

[119] *Light chain cloning.* The multiple cloning site of pcDNA3.1/Zeo+ (Invitrogen) was replaced by two different stuffers. The ?-stuffer provided restriction sites for insertion of a ?-leader (*Nhe*I / *Eco*RV), HuCAL®-scFv V?-domains (*Eco*RV / *Bsi*WI,) and the ?-chain constant region (*Bsi*WI / *Apa*I). The corresponding restriction sites in the ?-stuffer were *Nhe*I / *Eco*RV (?-leader), *Eco*RV / *Hpa*I (V?- domains), and *Hpa*I / *Apa*I (?-chain constant region). The ?-leader (EMBL Z00022) as well as the ?-leader (EMBL L27692) were both equipped with Kozak sequences. The constant regions of the human ?-(EMBL J00241) and ?-chain (EMBL M18645) were assembled by overlap extension-PCR as described above.

[120] *Generation of IgG-expressing CHO-cells.* CHO-K1 cells were co-transfected with an equimolar mixture of IgG heavy and light chain expression vectors. Double-resistant transfectants were selected with 600 µg/ml G418 and 300 µg/ml Zeocin (Invitrogen) followed by limiting dilution. The supernatant of single clones was assessed for IgG expression by capture-ELISA (see below). Positive clones were expanded in RPMI-1640 medium supplemented with 10% ultra-low IgG-FCS (Life Technologies). After adjusting the pH of the supernatant to 8.0 and sterile filtration, the solution was subjected to standard protein A column chromatography (Poros 20 A, PE Biosystems).

EXAMPLE 8

Design of the CDR3 libraries

[121] *V? positions 1 and 2.* The original HuCAL® master genes were constructed with their authentic N-termini: V?l1: QS (CAGAGC), V?l2: QS (CAGAGC), and V?l3: SY (AGCTAT). Sequences containing these amino acids are shown in WO 97/08320. During HuCAL® library construction, the first two amino acids were changed to DI to facilitate library cloning (*Eco*RI site). All HuCAL® libraries contain V?l genes with the *Eco*RV site GATATC (DI) at the 5'-end. All HuCAL® kappa genes (master genes and all genes in the library) contain DI at the 5'-end.

[122] *VH position 1.* The original HuCAL® master genes were constructed with their authentic N-termini: VH1A, VH1B, VH2, VH4, and VH6 with Q (=CAG) as the first amino acid and VH3 and VH5 with E (=GAA) as the first amino acid. Sequences containing these amino acids are shown in WO 97/08320. In the HuCAL® Fab 1 library, all VH chains contain Q (=CAG) at the first position.

[123] *V?1/V?3 position 85.* Because of the cassette mutagenesis procedure used to introduce the CDR3 library (Knappik *et al.*, *J. Mol. Biol. 296*, 57-86, 2000), position 85 of V?1 and V?3 can be either T or V. Thus, during HuCAL® scFv 1 library construction, position 85 of V?1 and V?3 was varied as follows: V?1 original, 85T (codon ACC); V?1 library, 85T or 85V (TRIM codons ACT or GTT); V?3 original, 85V (codon GTG); V?3 library, 85T or 85V (TRIM codons ACT or GTT); the same applies to HuCAL® Fab1.

[124] *CDR3 design.* All CDR3 residues which were kept constant are indicated in FIG. 1.

[125] *CDR3 length.* The designed CDR3 length distribution is as follows. Residues which were varied are shown in brackets (x) in FIG. 1. V kappa CDR3, 8 amino acid residues (position 89 to 96) (occasionally 7 residues), with Q90 fixed; V lambda CDR3, 8 to 10 amino acid residues (position 89 to 96) (occasionally 7-10 residues), with Q89, S90, and

D92 fixed; and VH CDR3, 5 to 28 amino acid residues (position 95 to 102) (occasionally 4-28), with D101 fixed.

EXAMPLE 9

Chronic carbon tetrachloride-induced liver fibrosis

[126] Sprague Dawley rats (200-220 g) are used in an *in vivo* model of liver fibrosis. To maximally induce microsomal metabolism of carbon tetrachloride metabolism, animals receive 1 g/l isoniazid with their drinking water starting one week before the administration of carbon tetrachloride. Carbon tetrachloride (1:1 in mineral oil) is administered orally every fifth day at a dose of 0.2 ml/100 g body weight. A human TIMP-1 antibody is administered intravenously, either once or repeatedly, during the period of carbon tetrachloride treatment. Necropsy is performed after 5-7 weeks of treatment. McLean *et al., Br. J. Exp. Pathol. 50,* 502-06, 1969.

[127] Transverse cylinders of liver tissue are cut from the right liver lobe, fixed in formaldehyde, and embedded in paraffin. The amount of fibrosis in the liver is indicated by the picrosirius red-stained fibrotic areas. Picrosirius-positive areas are determined in several centrilobular fields in each section. Parameters of color detection are standardized and kept constant throughout the experiment. The field are selected using a standardized grid which covers an area of 31 mm2. A Leica Quantimed 500 MC system is used for morphometry.

EXAMPLE 10

Hydroxyproline determination

[128] The method of Prockop & Udenfried, *Anal. Biochem. 1*, 228-39, 1960, can be used to determine hydroxyproline is liver tissues, with the following modifications. Liver specimens of 60-90 mg wet weight are dried and hydrolyzed in 6 N HCl at 100 °C for 17 h. The hydrolyzed material is dried and reconstituted in 5 ml of deionized water. Two

hundred microliters of this hydrolysate are mixed with 200 ml of ethanol and 200 ml chloramin T solution (0.7 % in citrate buffer [5.7 g sodium acetate, 3.75 g trisodium citrate, 0.55 g citric acid, 38.5 ml ethanol, made up to 100 ml with water]) and allowed to oxidize for 20 min at room temperature. Four hundred microliters of Ehrlich's reagent (12 g p-dimethylaminobenzldehyde in 40 ml ethanol and 2.7 ml H_2SO_4) are added. After incubation for 3 h at 35 °C, absorbance at 573 nm is measured.

EXAMPLE 11

Affinity determination by surface plasmon resonance measurements (BIAcore™)

[129] For affinity determination, monomeric fractions of affinity and SEC purified Fab fragments or purified IgG1 molecules were used. All experiments were conducted in HBS buffer at a flow rate of 20 µl/min at 25°C on a BIAcore™ instrument. Antigens in 100 mM sodium acetate pH 5.0 were coupled to a CM 5 sensor chip using standard EDC-NHS coupling chemistry. Applying 3-4 µl of 5 µg/ml TIMP-1 typically resulted in 500 resonance units for kinetic measurements. All sensograms were fitted globally using BIA evaluation software. For monovalent Fab fragments a monovalent fit (Langmuir binding) and for IgGs a bivalent fit was applied.

EXAMPLE 12

IC_{50} determination in human TIMP-1/human MMP-1 and rat TIMP-1/rat MMP-13 assay

[130] Purified Fab fragments or IgGs were used for IC_{50} determination. Antibodies were diluted in triplicate to the indicated concentrations in assay buffer containing 0.05% BSA. After addition of TIMP (final conc. 1.2 nM or 0.4 nM for modified in human TIMP-1/human MMP-1 assay), MMP (final conc. 1.2 nM or 0.4 nM for modified in human TIMP-1/human MMP-1 assay), and peptide substrate (final conc. 50 µM) and incubation for 1-3 h at 37°C, fluorescence at Ex320 nm/Em430 nm was measured.

[131] The following controls were included in the assay and used as reference values for IC_{50} determination:

A: MMP + substrate: this value was defined as 100% MMP activity in absence of antibody and TIMP.

B: MMP + TIMP + substrate: this value was defined as maximum inhibition achieved in the assay and calculated as a % of total MMP activity.

[132] To define the concentration of antibody that resulted in 50% reversal of inhibition (IC_{50}), the following procedure was used:

- The value for 50% reversal of inhibition (expressed as % activity MMP) was calculated as: $Y= [(A - B)/2] + B$.
- MMP activity was plotted against concentration of antibody in the assay.
- The concentration of antibody that results in 50% reversal of inhibition (Y) was read on the x-axis and defined as IC_{50}.
- Error bars in the graphs were derived from triplicate wells in one assay.
- Standard deviations for IC_{50} values were calculated from 3 independent assays.

EXAMPLE 13

Affinity maturation of selected Fab by stepwise exchange of CDR cassettes

[133] To increase affinity and biological activity of selected antibody fragments, CDR regions were optimized by cassette mutagenesis using trinucleotide directed mutagenesis (Virnekäs *et al.*, 1994). Fab fragments in expression vector pMORPH® x9 were cloned into phagemid vector pMORPH® _18 using *Eco*RI / *Xba*I restriction sites. CDR cassettes containing several diversified positions were synthesized and cloned into Fab fragments in pMORPH® _18 using unique restriction sites (Knappik *et al.*, 2000). Affinity

maturation libraries were generated by transformation into *E. coli* TOP10F, and phage were prepared as described above. Phage displaying Fab fragments with improved affinity were selected by 2-3 rounds solution panning using stringent washing conditions (*e.g.*, competition with 1 μM non-biotinylated antigen or washing for up to 48 h with frequent buffer exchange) and limited amounts of antigen (0.04 – 4 nM). Seventeen human TIMP-1 antibodies were tested for affinity to human TIMP-1 (with some tested for affinity to rat TIMP-1) using a BIAcore™ assay. The K_d of these antibodies for human TIMP-1 and rat TIMP-1 are shown in Table 1.

Table 1. Overview of species cross-reactive Fab

Fab	Monovalent K_D human TIMP-1	Monovalent K_D rat TIMP-1	IC_{50} in human protease assay	IC_{50} in rat protease assay
MS-BW-25	25+/- 16 nM*	4517 +/- 2400 nM	115 +/- 15 nM	> 300 nM
MS-BW-27	~74 nM	~ 3200 nM	Non blocking	
MS-BW-21	520+/- 20 nM	36 +/- 2 nM	> 300 nM	67 +/- 5nM
MS-BW-38	~3 nM	~353 nM	~11 nM	> 300 nM
MS-BW-39	~7500 nM	~108 nM	> 100 nM	> 100 nM

* In cases were standard deviations are given, three independent measurements were done with Fab from three different protein expressions/purifications.

~ Indicates preliminary data, in cases where measurement was done only once.

EXAMPLE 14

Screening for Fab with improved off-rates by koff ranking using surface plasmon resonance

[134] Phage eluted after solution panning were used to infect *E. coli* TG-1 and plated on agar plates containing 34 μg/ml chloramphenicol. Clones were picked into 96 well plates and used to produce Fab fragments. On the same plate, parental clones were inoculated as controls. Soluble Fab was extracted from the periplasm by osmotic shock (Ausubel *et al.*, 1998) and used for koff ranking in BIAcore™.

[135] All measurements were conducted in HBS buffer at a flow rate of 20 μl/min at 25°C on a BIAcore™ instrument. Antigens in 100 mM sodium acetate pH 4.5 were coupled to a CM 5 sensor chip using standard EDC-NHS coupling chemistry. Applying 10 μl of 25 μg/ml TIMP-1 typically resulted in 5000 resonance units for koff ranking. All sensograms were fitted using BIA evaluation software. Clones with improved off rate were selected by comparison to parental clones.

EXAMPLE 15

Generation of species cross-reactive antibodies

[136] To maximize the likelihood of obtaining blocking antibodies that are cross-reactive between human and rat TIMP-1, alternating pannings were carried out on rat and human protein. Additionally, all antibodies selected by pannings on solely the human or rat TIMP-1 protein were analyzed for cross-reactivity in order to check for cross-reactive antibodies that might be selected by chance. Antibodies selected from these pannings were analyzed for cross-reactivity in ELISA using crude *E. coli* extracts. Cross-reactive antibodies in this assay were subjected to expression in 1-liter scale followed by purification. Purified antibodies were tested for cross-reactivity in BIAcore™ and protease assays (Table 1).

[137] As shown in Table 1, a total of five different Fab cross-reactive with human and rat TIMP-1 were generated. BIAcore™ measurements revealed that although these antibodies clearly bind to human and rat TIMP-1, affinities for both species differ by at least a factor of 50. An antibody used for human therapy or in an animal model should have an affinity to the target protein in the low nanomolar, preferably in the sub-nanomolar range. As none of the above-described antibodies had affinities in this range for both species, these antibodies were not considered useful for further experiments or development.

EXAMPLE 16

Generation of blocking antibodies against human TIMP-1

[138] To generate blocking antibodies against human TIMP-1, the HuCAL®-Fab 1 library was used for antibody selection (AutoPan®) on purified TIMP-1 protein followed by subcloning and expression of the selected Fab fragments in *E. coli*. Crude antibody-containing *E. coli* extracts were used for primary antibody characterization in ELISA (AutoScreen®). Purified Fab proteins were subjected to further characterization in ELISA, TIMP-1/MMP-1 assay and BIAcore™. A total of 6100 clones were analyzed in AutoScreen®, 670 of them showed binding to human TIMP-1. Sequence analysis revealed that in total seven unique antibody clones had been selected (Table 2). For these seven Fab clones, the affinities measured in BIAcore™ were in the range of 10 – 180 nM (Table 4). When tested in the human protease assay, five of them were able to block the interaction between human TIMP-1 and MMP-1. The concentration of monovalent Fab needed to reverse the inhibitory effect of human TIMP-1 on human MMP-1 activity by 50% (IC_{50}) was in the range of 11 - 100 nM (Table 2). The most active Fab clones are MS-BW-3 (K_d 13 nM; IC_{50} 11 nM) and MS-BW-28 (K_d 10 nM; IC_{50} 22 nM).

[139] A striking feature of antibodies selected against human TIMP-1 is that they all exhibit the combination VH312 and a relatively short VH-CDR3 region, predominantly four amino acids (see Table 2). The HCDR3 cassettes assembled for the HuCAL®-Fab 1 library

were designed to achieve a length distribution ranging from 5 to 28 amino acid residues. A four amino acid HCDR3 can occur in the library due to TRIM deletion, but is considered a very rare event. Another remarkable feature was the high degree of sequence homology among the selected LCDR3 sequences.

Table 2. Overview of anti-human TIMP-1 Fab

Fab	Framework + CDR 3 sequence				Monovalent K_D to human TIMP-1	IC_{50} in human protease assay
	VH	HCDR3	VL	LCDR3		
MS-BW-1	H3	FMDI, SEQ ID NO:1	?2	QSYDYQQFT, SEQ ID NO:44	65+/-13 nM*	>100 nM
MS-BW-2	H3	GFDY, SEQ ID NO:2	?2	QSYDFKTYL, SEQ ID NO:45	180+/-28 nM	>100 nM
MS-BW-3	H3	FLDI, SEQ ID NO:3	?2	QSYDFLRFS, SEQ ID NO:46	13+/-2 nM	11+/-2nM
MS-BW-25	H3	TFPIDADS, SEQ ID NO:4	?2	QSYDFINVI, SEQ ID NO:47	25+/-16nM	115+/-15 nM
MS-BW-26	H3	GHVDY, SEQ ID NO:5	?2	QSYDFVRFM, SEQ ID NO:48	~100 nM	non blocking
MS-BW-27	H3	YWRGLSFDI, SEQ ID NO:6	?2	QSYDFYKFN, SEQ ID NO:49	~74	non blocking
MS-BW-28	H3	FFDY, SEQ ID NO:7	?2	QSYDFRRFS, SEQ ID NO:50	10+/-1 nM	22+/-2nM

* In cases were standard deviations are given, three independent measurements were done with Fab from three different protein expressions/purifications.

~ Indicates preliminary data, in cases where measurement was done only once.

EXAMPLE 17

Increasing the affinity of selected anti-human TIMP-1 antibodies

[140] In order to increase the affinity of monovalent anti-human TIMP-1 Fab fragments to the sub-nanomolar range, a step-wise affinity maturation approach was applied, by optimizing CDR sequences and keeping framework regions constant.

Affinity maturation by light chain cloning

[141] The CDR3 sequences of the two antibody fragments with highest affinity (MS-BW-3 and MS-BW-28) had the remarkable feature of an unusually short four amino acid HCDR3 sequence. Furthermore, each Fab had a very similar LCDR3 sequence. This indicates that MS-BW-3 and MS-BW-28 bind to the same epitope and that this epitope might tolerate only a very small subset of CDR3 sequences. As a four amino acid HCDR3 is a very rare event in the library, it can be anticipated that in the initial library not all possible combinations of the short HCDR3 and the preferred LCDR3 are present. Therefore, it was considered that another combination of the selected HCDR3 and LCDR3 sequences might increase the affinity. For this approach, the heavy chain of MS-BW-3 and MS-BW-28 were paired with the light chains of MS-BW-1, -2, -3, -25, -26, -27, and -28 by cloning.

[142] The resulting constructs were transformed into *E. coli* and expressions/purifications in 1-liter scale were performed. Of the 12 new constructs, 10 resulted in functional Fab molecules. These were analyzed in BIAcore™ and human protease assay as summarized in Table 3. The best antibody named MS-BW-44 had a monovalent affinity of 2 nM and an IC50 of 4 nM (FIG. 7) and was thus improved by a factor of 6.5 (K_d) or 2.75 (IC_{50}).

Table 3. Overview of Fab derived from light chain cloning

Fab	Framework + CDR 3 sequence				Monovalent K_D to human TIMP-1	IC_{50}* in human protease assay
	VH	HCDR3	VL	LCDR3		
MS-BW-40	H3	FLDI, SEQ ID NO:3	?2	QSYDYQQFT, SEQ ID NO:44	~49 nM	> 100 nM
MS-BW-41	H3	FLDI, SEQ ID NO:3	?2	QSYDFKTYL, SEQ ID NO:45	~6 nM	29+/-6nM
MS-BW-43	H3	FLDI, SEQ ID NO:3	?2	QSYDFINVI, SEQ ID NO:47	~65 nM	> 100 nM
MS-BW-44	H3	FLDI, SEQ ID NO:3	?2	QSYDFVRFM, SEQ ID NO:48	2 +/- 0.4 nM*	4+/-1 nM
MS-BW-45	H3	FLDI, SEQ ID NO:3	?2	QSYDFYKFN, SEQ ID NO:49	8 +/- 5 nM	9+/-3 nM
MS-BW-46	H3	FLDI, SEQ ID NO:3	?2	QSYDFRRFS, SEQ ID NO:50	6 +/- 3 nM	4+/-0.5 nM
MS-BW-47	H3	FFDY, SEQ ID NO:7	?2	QSYDYQQFT, SEQ ID NO:44	~152 nM	> 100 nM
MS-BW-49	H3	FFDY, SEQ ID NO:7	?2	QSYDFKTYL, SEQ ID NO:45	~21 nM	> 100 nM
MS-BW-51	H3	FFDY, SEQ ID NO:7	?2	QSYDFINVI, SEQ ID NO:47	~7 nM	7+/-1 nM
MS-BW-52	H3	FFDY, SEQ ID NO:7	?2	QSYDFVRFM, SEQ ID NO:48	~11 nM	9+/-1 nM

* In cases were standard deviations are given, three independent measurements were done with Fab from three different protein expressions/purifications.

~ Indicates preliminary data, in cases where measurement was done only once.

Affinity maturation by optimizing HCDR1 and HCDR2

[143] In the HuCAL®-Fab 1 library, only the CDRs HCDR3 and LCDR3 are diversified to a high extent. Although it is known from crystallographic studies that amino acids from these two CDRs make most of the antibody antigen contacts, the residual four CDRs are also important for antigen binding. However, their contribution to the binding energy can vary from antibody to antibody. In the HuCAL®-Fab 1 library those CDRs exhibit only a limited variability due to the presence of the different master frameworks (Knappik *et al.*, 2000). In order to improve the affinity of the selected antibodies, an affinity maturation approach by randomizing HCDR1 and HCDR2 was applied. For this approach two affinity maturation libraries based on MS-BW-44 cloned into phage display vector pMORPH® 18 were created. In library 1, only HCDR2 of MS-BW-44 was diversified using "TRIM technology" as described in Virnekäs *et al.*, *Nucl. Acids. Res. 22*, 5600-07, 1994; Knappik *et al.*, *J. Mol. Biol. 296*, 57-86, 2000. In library 2, both HCDR1 and HCDR2 were diversified using the TRIM technology. In both cases, phage antibody libraries comprising 1 x 10^8 different clones were obtained. Both libraries were mixed and used as input for a modified AutoPan® procedure. In order to select antibodies having an increased affinity to human TIMP-1, solution panning using limiting amounts of biotinylated antigen and stringent washing conditions were applied. Antibody off rates were ranked by BIAcore™ using crude *E. coli* extracts of selected antibodies. Clones with slower off rate than parental clone MS-BW-44 were subjected to 1-liter scale expression and purification. Purified Fab were analyzed in BIAcore™ and human protease assay (Table 4).

Table 4. Comparison of Fab derived from HCDR1 and HCDR2 optimization with parental clone MS-BW-44

Fab	Monovalent K_D to human TIMP-1	IC_{50} in human protease assay*
MS-BW-44	2 +/- 0.4 nM	2 +/- 0.5 nM
MS-BW-44-2	0.5 +/- 0.2 nM	0.4 +/- 0.3 nM
MS-BW-44-6	0.6 +/- 0.2 nM	0.2 +/- 0.1 nM

* IC_{50} values derived from modified protease assay using decreased amounts of TIMP-1 and MMP-1 (0.4 nM each).

[144] Clone MS-BW-44-2 was derived from library 1 thus having a modified HCDR2 cassette. Its affinity measured by BIAcore™ was 0.5 nM. Clone MS-BW-44-6 was derived from library 2 having a modified HCDR 1 and HCDR 2 cassette and the affinity measured by BIAcore™ was 0.6 nM. A sequence comparison between the affinity matured antibodies and their parental clones is shown in Table 8.

Table 8: Overview and sequence comparison of affinity matured Fab fragments against human TIMP-1. Sequence changes compared to parental Fab fragments (bold) are italicized

Clone	VH				VL				Monov. K_D to human TIMP-1 (nM)	IC_{50} in human protease assay (nM)
MS-BW-	Frame-work	HCDR1 sequence (SEQ ID NO:)	HCDR2 sequence (SEQ ID NO:)	HCDR3 sequence (SEQ ID NO:)	Framework	LCDR1 sequence (SEQ ID NO:)	LCDR2 sequence (SEQ ID NO:)	LCDR3 sequence (SEQ ID NO:)		
3	VH3	GFTFSSYAMS (355)	**AISGSGGSTYYADSVKG** (357)	FLDI (3)	VL2	**TGTSSDVGGYNYVS** (363)	**DVSNRPS** (364)	**QSYDFLRFS** (47)	13 +/- 2	11 +/- 2
44	VH3	GFTFSSYAMS (355)	AISGSGGSTYYADSVKG (357)	FLDI (3)	VL2	TGTSSDVGGYNYVS (363)	DVSNRPS (364)	QSYDF*V*RF*M* (48)	2 +/- 0.4	4 +/- 1
44-6	VH3	GFTF*N*SYAMS (356)	*V*ISG*N*G*SN*TYYADSVKG (358)	FLDI (3)	VL2	TGTSSDVGGYNYVS (363)	DVSNRPS (364)	QSYDF*V*RF*M* (48)	0.6 +/- 0.2	0.2 +/- 0.1 *
44-2	VH3	GFTFSSYAMS (355)	*G*ISG*N*G*VLIF*YADSVKG (359)	FLDI (3)	VL2	TGTSSDVGGYNYVS (363)	DVSNRPS (364)	QSYDF*V*RF*M* (48)	0.5 +/- 0.2	0.4 +/- 0.3 *
44-2-4	VH3	GFTFSSYAMS (355)	*G*ISG*N*G*VLIF*YADSVKG (359)	*GLMDY* (360)	VL2	TGTSSDVGGYNYVS (363)	DVSNRPS (364)	QSYDF*V*RF*M* (48)	0.2 +/- 0.02	0.2 +/- 0.1 *
44-2-15	VH3	GFTFSSYAMS (355)	*G*ISG*N*G*VLIF*YADSVKG (359)	*WFDH* (361)	VL2	TGTSSDVGGYNYVS (363)	DVSNRPS (364)	QSYDF*V*RF*M* (48)	0.3 +/- 0.1	0.2 +/- 0.1 *
44-2-16	VH3	GFTFSSYAMS (355)	*G*ISG*N*G*VLIF*YADSVKG (359)	*WFDV* (362)	VL2	TGTSSDVGGYNYVS (363)	DVSNRPS (364)	QSYDF*V*RF*M* (48)	0.5 +/- 0.2	0.3 +/- 0.1 *
44-6-1	VH3	GFTF*N*SYAMS (356)	*V*ISG*N*G*SN*TYYADSVKG (358)	FLDI (3)	VL2	TGTSSDVGGYNYVS (363)	DVSNRPS (364)	QSYDF*I*RF*M* (365)	0.2 +/- 0.04	0.2 +/- 0.1 *

* IC_{50} values derived from modified protease assay using decreased amounts of TIMP-1 and MMP-1; IC_{50} of MS-BW-44 is 2 nM under these conditions

[145] When initially analyzed in the human TIMP-1/MMP-1 assay, it was not possible to distinguish a Fab with a sub-nanomolar affinity from a Fab with 1 nM affinity, most likely because the concentration of Fab required to reverse the inhibitory effect of human TIMP-1 on human MMP-1 activity by 50% was below the concentration of total TIMP-1 in the assay. When a modified assay was used with concentrations of TIMP-1 and MMP-1 decreased from 1.2 nM to 0.4 nM, it was possible to distinguish a 2 nM Fab from a sub-nanomolar Fab (Table 4, FIG. 8). Using this modified protease assay, MS-BW-44-2 and MS-BW-44-6 had IC_{50} values of 0.4 nM and 0.2 nM respectively. Parental clone MS-BW-44 had an IC_{50} of 2 nM under these conditions. Thus, by this affinity maturation approach, an affinity gain of a factor of 5 (K_d) or 5-10 (IC_{50}) was achieved.

Affinity maturation by optimizing HCDR3

[146] As mentioned above, amino acid residues in HCDR3 and LCDR3 are considered the most important for antigen binding. Taking into account that a four amino acid HCDR3 was not planned in the design of HuCAL®-Fab 1 and thus only occurs as a rare case due to a TRIM deletion, probably not all possible combinations of the four amino acids in HCDR3 were represented in the original HuCAL®-Fab 1 library. Therefore, an affinity maturation library was constructed with four and five amino acid HCDR3 maturation cassettes inserted into Fab derived from the previous maturation cycle (among them MS-BW-44-2 and MS-BW-44-6). The obtained affinity maturation library had a diversity of 1×10^8 clones, therefore theoretically covering all possible four and five amino acid HCDR3 variations. Applying very stringent panning conditions, the best antibody identified, MS-BW-44-2-4, had an affinity measured by BIAcore™ of 0.2 nM and an IC_{50} in human TIMP-1/MMP-1 assay of 0.2 nM. A sequence comparison between the affinity matured antibodies and their parental clones is shown in Table 8. The improvement factor gained by this affinity maturation approach is 2.5 with respect to the affinity and 2 with respect to the IC_{50}.

Affinity maturation by optimizing LCDR3

[147] As an alternative approach, a maturation strategy was used to further optimize the light chain CDR3 sequence. This was due to the fact that in the first maturation cycle where light chain exchange cloning between selected antibodies was applied, only a very limited subset of sequence variation had been exploited. Therefore, a maturation library was constructed in which, using TRIM technology, a diversified LCDR3 cassette was inserted into Fab derived from HCDR1 and HCDR2 optimization (among them MS-BW-44-2 and MS-BW-44-6). The best Fab identified with this maturation strategy was MS-BW-44-6-1 with an affinity measured by BIAcore™ of 0.15 nM and an IC_{50} in a human TIMP-1/MMP-1 assay of 0.2 nM. A sequence comparison between the affinity matured antibody and its parental clones is shown in Table 8. The improvement factor gained by this maturation approach is 4 with respect to affinity. A further improvement of the IC_{50} in the protease assay could not be measured due to limitations in the assay.

[148] As a result of a step-wise affinity maturation approach using four different maturation strategies, the monovalent affinity of an anti-human TIMP-1 specific Fab fragment was improved by a factor of 87 and its activity in human TIMP-1/MMP-1 assay by a factor of 55. The decision for defining the best Fab fragment has been made on the basis of K_d measurements using BIAcore™, as this method proved to be reliable for ranking antibodies with sub-nanomolar affinities, whereas the sensitivity of the human TIMP-1/MMP-1 assay was considered not suitable to rank activity of the best Fabs in the sub-nanomolar range with respect to each other.

[149] The best Fab MS-BW-44-6-1 has an affinity measured by BIAcore™ of 0.15 nM and an IC_{50} in human TIMP-1/MMP-1 assay of 0.2 nM. Compared to its parental clone, MS-BW-3, it has optimized LCDR3, HCDR1 and HCDR2 sequences.

EXAMPLE 18

Cross reactivity of selected anti-human TIMP-1 Fab with TIMP-2, TIMP-3, and TIMP-4

[150] TIMP-1 belongs to a family of closely related protease inhibitors all binding to various members of the MMP family of proteases. To date there are four human TIMP proteins described. To investigate potential cross-reactivity of antibody fragments selected against human TIMP-1 with other members of the human TIMP family, an ELISA was performed in which binding of antibody fragments to immobilized purified human TIMP-1, -2, -3 or –4 was analyzed (FIG. 10). Antibody fragments binding to immobilized human TIMP-1 showed no binding to human TIMP-2, -3, -4 above background level when compared to unrelated control protein BSA.

EXAMPLE 19

Generation of blocking antibodies against rat TIMP-1

[151] To generate blocking antibodies against rat TIMP-1, the HuCAL®-Fab 1 library was used for antibody selection (AutoPan®) on immobilized rat TIMP-1 followed by subcloning and expression of the selected Fab fragments in *E. coli*. Crude antibody-containing *E. coli* extracts were used for primary antibody characterization in ELISA (AutoScreen®). Purified Fab proteins were subjected to further characterization in ELISA, protease assays, and BIAcore™. Of the 8,450 selected clones were analyzed in AutoScreen®, 750 of them showed binding to rat TIMP-1. Sequence analysis revealed that in total 36 unique Fab clones specific for rat TIMP-1 were enriched during selection (Table 7). Their affinities were measured by BIAcore™ and were found to be in the range of 9 – 1000 nM (Table 7). When tested in the rat protease assay, all but one of them were able to block the interaction between rat TIMP-1 and rat MMP-13 (Table 7). The concentration of monovalent Fab needed to reverse the inhibitory effect of rat TIMP-1 on rat MMP-13 activity by 50% (IC_{50}) was in the range of 7 - 300 nM. The most active Fab

clones are MS-BW-14 (K_d 10 nM; IC_{50} 14 nM), MS-BW-17 (K_d 13 nM; IC_{50} 11 nM), and MS-BW-54 (K_d 9 nM; IC_{50} 7 nM).

Table 7. Overview of anti-rat TIMP-1 Fab

Fab	Framework + CDR 3 sequence				Monovalent K_D to rat TIMP-1	IC_{50}* in rat protease assay
	VH	HCDR3	VL	LCDR3		
MS-BW-5	H1A	GLYWAVYPYFDF, SEQ ID NO:8	?1	QSRDFNRGP, SEQ ID NO:51	~210 nM	non blocking
MS-BW-6	H3	LDTYYPDLFDY, SEQ ID NO:9	?1	QSYDQRKW, SEQ ID NO:52	~68 nM	~100 nM
MS-BW-7	H1A	TYYYFDS, SEQ ID NO:10	?3	QQLYGTVS, SEQ ID NO:53	~168 nM	> 300 nM
MS-BW-9	H3	YMAYMAEAIDV, SEQ ID NO:11	?1	QSYDGFKTH, SEQ ID NO:54	~256 nM	> 300 nM
MS-BW-10	H1B	LVGIVGYKPDELLYFDV, SEQ ID NO:12	?3	QSYDYSLL, SEQ ID NO:55	~200 nM	~ 30 nM
MS-BW-11	H3	YGAYFGLDY, SEQ ID NO:13	?3	QSYDFNFH, SEQ ID NO:56	~200 nM	>300 nM
MS-BW-12	H6	GYADISFDY, SEQ ID NO:14	?2	QSYDMIARYP, SEQ ID NO:57	~419 nM	>300 nM
MS-BW-13	H3	YYLLLDY, SEQ ID NO:15	?3	QSWDIHPFDV, SEQ ID NO:58	~939 nM	not tested
MS-BW-14	H1A	WSDQSYHYYWHPYFDV, SEQ ID NO:16	?1	QSWDLEPY, SEQ ID NO:59	10 +/- 5 nM	14+/-3 nM
MS-BW-15	H3	LIGYFDL, SEQ ID NO:17	?2	QSYDVLDSE, SEQ ID NO:60	~80 nM	~ 200 nM
MS-BW-17	H5	LTNYFDSIYYDH, SEQ ID NO:18	?2	QSYDPSHPSK, SEQ ID NO:61	13 +/- 3 nM	11+/-3 nM
MS-BW-18	H5	LVGGGYDLMFDS, SEQ ID NO:19	?2	QSYDDMQF, SEQ ID NO:62	~153 nM	> 300 nM
MS-BW-19	H5	YVTYGYDDYHFDY, SEQ ID NO:20	?2	QSWDINHAI, SEQ ID NO:63	~187 nM	> 300 nM
MS-BW-20	H1A	SGYLDY, SEQ ID NO:21	?2	QSYDYYDYG, SEQ ID NO:64	~70 nM	> 300 nM

MS-BW-21	H1A	YIGYTNVMDIRPGYFLDY, SEQ ID NO:22	?3	QQANDFPI, SEQ ID NO:65	36 +/- 2 nM	67+/-5nM
MS-BW-22	H5	FRAYGDDFYFDV, SEQ ID NO:23	?2	QSWDNLKMPV, SEQ ID NO:66	35 nM	65+/-11 nM
MS-BW-23	H1B	JMWSDYGQLVKGGDI, SEQ ID NO:24	?2	QSYDVFPINR, SEQ ID NO:67	~207 nM	> 300 nM
MS-BW-24	H5	YYVTDTAYFDY, SEQ ID NO:25	?2	QSDLYFP, SEQ ID NO:68	23 nM	20+/-1 nM
MS-BW-29	H5	HDFDGSIFMDF, SEQ ID NO:26	? 2	QSYDVTPR, SEQ ID NO:69	~214 nM	>100 nM
MS-BW-30	H5	YAGHQYEFFFDF, SEQ ID NO:27	? 3	QSRDPVGFP, SEQ ID NO:70	~36 nM	>100 nM
MS-BW-31	H5	LYADADIYFDY, SEQ ID NO:28	? 2	QSYDLSPR, SEQ ID NO:71	~13 +/- 9 nM	>100 nM
MS-BW-32	H1A	TKYVGSEDV, SEQ ID NO:29	? 2	QSYDFSHYFF, SEQ ID NO:72	~92 nM	> 100 nM
MS-BW-36	H5	YRYPHMFDF, SEQ ID NO:30	? 3	QSYDLRYSH, SEQ ID NO:73	~42 nM	~75 nM
MS-BW-37	H5	LFAGLELYFDY, SEQ ID NO:31	? 2	QSYDLRNR, SEQ ID NO:74	10 +/- 9 nM	>100 nM
MS-BW-38	H3	GGFFNMDY, SEQ ID NO:32	? 2	QSYDFTYGS, SEQ ID NO:75	~353 nM	>300 nM
MS-BW-39	H1A	GYIPYHLFDY, SEQ ID NO:33	?3	QQFNDSPY, SEQ ID NO:76	~108 nM	>100 nM
MS-BW-54	H5	YYGFEYDLLFDN, SEQ ID NO:34	? 2	QSYDISGYP, SEQ ID NO:77	9 +/- 1 nM	7 nM
MS-BW-55	H1B	ITYIGYDF, SEQ ID NO:35	? 2	QSRDLYYVYY, SEQ ID NO:78	~23 nM	~ 100 nM
MS-BW-56	H1A	QEWYMDY, SEQ ID NO:36	? 3	QSYDRSMW, SEQ ID NO:79	~170 nM	> 100 nM
MS-BW-57	H5	LYPEDLIYFDY, SEQ ID NO:37	? 2	QSWDVQTDK, SEQ ID NO:80	~39 nM	~60 nM
MS-BW-58	H6	WMTPPGHYYGYTFDV, SEQ ID NO:38	? 3	QSWDPSHYY, SEQ ID NO:81	~138 nM	not tested
MS-BW-59	H5	LRVHDYAMYFDL, SEQ ID NO:39	? 2	QSYDIMPER, SEQ ID NO:82	~15 nM	30 +/- 5nM

MS-BW-60	H5	FVSYNGSVPYFDY, SEQ ID NO:40	? 2	QSMDFRLMH, SEQ ID NO:83	~30 nM	> 100 nM
MS-BW-61	H5	IIGDYVIFFDV, SEQ ID NO:41	? 2	QSFDMIHPY, SEQ ID NO:84	~51 nM	> 100 nM
MS-BW-62	H5	LFTYPFLYFDV, SEQ ID NO:42	? 2	QSDFPVM, SEQ ID NO:85	~36 nM	19 +/- 2
MS-BW-63	H5	ILTGHVLLFDY, SEQ ID NO:43	? 2	QSDNPYL, SEQ ID NO:86	~14 nM	20 +/- 1nM

* In cases were standard deviations are given, three independent measurements were done with Fab from three different protein expressions/purifications.

~ Indicates preliminary data, in cases where measurement was done only once.

EXAMPLE 20

Increasing the affinity of selected anti-rat TIMP-1 antibodies

[152] Affinity maturation was applied to increase the affinity of monovalent anti-rat TIMP-1 Fab fragments to the sub-nanomolar range. No clear sequence homology could be identified among the light chain CDR3 sequences of the selected antibody fragments, indicating that an optimal light chain CDR3 sequence was probably not present or had not been selected from the original HuCAL®-Fab 1 library. We therefore started with modification of LCDR3 to increase the affinity of Fabs.

[153] Two affinity maturation libraries based on MS-BW-14, -17, and -54 cloned into phage display vector pMORPH® 18 were created. In library 1, only LCDR3 was diversified using TRIM technology, as described in Virnekäs *et al.*, *Nucl. Acids. Res. 22*, 5600-07, 1994; Knappik *et al.*, *J. Mol. Biol. 296*, 57-86, 2000. In library 2, LCDR1, LCDR2, and LCDR3 were diversified simultaneously using the TRIM technology, while the connecting framework regions were kept constant. In both cases, phage antibody libraries comprising 3 x 10^8 different clones were obtained. Both libraries were mixed and used as input for a modified AutoPan® procedure. To select antibodies having an increased affinity to rat TIMP-1, solution panning using limiting amounts of biotinylated antigen and stringent washing conditions were applied.

[154] Antibody-off-rates were ranked by BIAcore™ using crude *E. coli* extracts. Clones with slower off rate than parental clones MS-BW-14, -17, or -54 were subjected to expression and purification in 1-liter scale. Purified Fab were analyzed in BIAcore™ and rat protease assays (Table 6). MS-BW-17-1 (K_d 0.8 nM, IC_{50} 1.6 nM), MS-BW-17-2 (K_d 1.3 nM, IC_{50} 1.1 nM), and MS-BW-17-3 (K_d 1.9 nM, IC_{50} 3 nM) were derived from affinity maturation library 1 having an optimized LCDR3 sequence, whereas MS-BW-

54-1 (K_d 2 nM, IC_{50} 3 nM) was derived from affinity maturation library 2 having an optimized LCDR1, -2, and -3 sequence (Table 9).

Table 9. Overview and sequence comparison of affinity matured Fab fragments against rat TIMP-1. Sequence changes compared to parental Fab fragments (bold) are italicized.

Clone (MS-BW-)	VH				VL				Monov. K_D to rat TIMP-1 (nM)	IC_{50} in rat protease assay (nM)
	Frame-work	HCDR1 sequence (SEQ ID NO:)	HCDR2 sequence (SEQ ID NO:)	HCDR3 sequence (SEQ ID NO:)	Frame-work	LCDR1 sequence (SEQ ID NO:)	LCDR2 sequence (SEQ ID NO:)	LCDR3 sequence (SEQ ID NO:)		
14	VH1A	**GGTFSSYAIS** (366)	**GIIPIFGTANYAQKFQG** (368)	**WSDQSYHYYWHPYFDV** (370)	VL1	**SGSSSNIGSNYVS** (371)	**LMIYDNNQRPS** (373)	**QSWDLEPY** (59)	10 +/- 5	14 +/- 3
17	VH5	**GYSFTSYWIG** (367)	**IIYPGDSDTRYSPSFQG** (369)	**LTNYFDSIYYDH** (18)	VL2	**TGTSSDVGGYNYVS** (363)	**LMIYDVSNRPS** (374)	**QSYDPSHPSK** (61)	13 +/- 3	11 +/- 3
54	VH5	**GYSFTSYWIG** (367)	**IIYPGDSDTRYSPSFQG** (369)	**YYGFEYDLLFDN** (34)	VL2	**TGTSSDVGGYNYVS** (363)	**LMIYDVSNRPS** (374)	**QSYDISGYP** (77)	9 +/- 1	7
17-1	VH5	GYSFTSYWIG (367)	IIYPGDSDTRYSPSFQG (369)	LTNYFDSIYYDH (18)	VL2	TGTSSDVGGYNYVS (363)	LMIYDVSNRPS (374)	Q*AFDVAPNG*K (376)	0.8	1.6
17-2	VH5	GYSFTSYWIG (367)	IIYPGDSDTRYSPSFQG (369)	LTNYFDSIYYDH (18)	VL2	TGTSSDVGGYNYVS (363)	LMIYDVSNRPS (374)	Q*AFAVMPNV*E (377)	1.3	1.1
17-3	VH5	GYSFTSYWIG (367)	IIYPGDSDTRYSPSFQG (369)	LTNYFDSIYYDH (18)	VL2	TGTSSDVGGYNYVS (363)	LMIYDVSNRPS (374)	QS*FTVSPGA*D (378)	1.9	3
54-1	VH5	GYSFTSYWIG (367)	IIYPGDSDTRYSPSFQG (369)	YYGFEYDLLFDN (34)	VL2	TGTSSD*L*GGYNYVS (372)	LMIY*AGN*NRPS (375)	QAYDSSGYP (379)	2	3

[155] The improvement gained by these different one-step maturation strategies was up to a factor of 16.3 with regard to affinity and 10 with regard to functional activity in the protease assay.

EXAMPLE 21

Conversion of anti-TIMP-1 Fab fragments into human IgG_1 molecules for use in the rat model of chronic carbon tetrachloride-induced liver fibrosis

[156] Anti-TIMP-1 Fab fragments were converted into human IgG1 molecules to create antibody molecules with prolonged *in vivo* half-lives for the use in the rat model of chronic carbon tetrachloride-induced liver fibrosis. This was done by cloning the heavy and light chain variable regions of the Fab into two separate vectors for mammalian IgG_1 expression (Krebs *et al.*, 2001)

[157] Anti-rat TIMP-1 clone MS-BW-14 was chosen for the first *in vivo* study, and IgG_1 protein was produced by transient expression. Anti-human TIMP-1 clone MS-BW-3 was selected as a negative control IgG_1 and was also produced by transient expression. Purified IgG_1 proteins MS-BW-14 and MS-BW-3 were subjected to quality control in BIAcore™ and rat TIMP-1/rat MMP-13 assays. Bivalent affinity for rat TIMP-1 measured in BIAcore™ (chip density 500 RU, fitting model for bivalent analyte) is 0.2 nM for MS-BW-14, compared to 13 nM for the corresponding monovalent Fab fragment. This increase in affinity for the IgG_1 is due to the avidity effects caused by binding of bivalent IgG_1 to immobilized rat TIMP-1 protein on the BIAcore™ chip. As expected, the negative control IgG_1 MS-BW-3 showed no binding to rat TIMP-1 but bound to human TIMP-1 with a bivalent affinity of approximately 0.4 nM.

[158] FIG. 12 shows the activity of MS-BW-14 Fab and IgG_1 and MS-BW-3 IgG_1 in a rat TIMP-1/rat MMP-13 assay. The IC_{50} of MS-BW-14 Fab and IgG_1 are nearly identical. The avidity effect seen in BIAcore™ does not occur in this assay because, in contrast to

the BIAcore™ experiment, this assay is based on a monovalent interaction in solution between TIMP-1 and the IgG_1. As expected, MS-BW-3 has no effect on rat TIMP-1 binding to rat MMP-13 and thus is a suitable negative control for a rat *in vivo* study.

[159] Affinity matured clone MS-BW-17-1 was then converted from a monovalent Fab fragment to a bivalent IgG_1. Protein was produced by stable transfection. Purified protein was subjected to quality control in BIAcore™ and rat TIMP-1/rat MMP-13 assays (FIG. 13). In BIAcore™ an increased bivalent affinity (avidity) of 0.04 nM for IgG_1 compared to 0.8 nM for monovalent Fab fragment was seen, whereas the activity in the rat TIMP-1/rat MMP-13 assay was comparable for IgG_1 and Fab as expected.

EXAMPLE 22

Cross-reactivity of anti-rat TIMP-1 IgG_1 MS-BW-17-1 with mouse TIMP-1

[160] Species cross-reactivity of MS-BW-17-1 IgG_1 and Fab with mouse TIMP-1 was determined by BIAcore™ to investigate the feasibility of alternative *in vivo* models that use mice instead of rats. Although MS-BW-17-1 clearly bound to mouse TIMP-1 immobilized to the chip surface, the affinity of both Fab (180 nM) and IgG_1 (9 nM) was 225-fold weaker than the affinity to rat TIMP-1. As the interaction between mouse TIMP-1 and BW-17-1 IgG_1 in serum is most likely monovalent, the affinity of BW-17-1 Fab probably reflects the "real" affinity of this interaction. Therefore, the Fab affinity value should be considered when calculating the feasibility of using BW-17-1 IgG_1 in a mouse *in vivo* study.

EXAMPLE 23

Effect of Timp-1 antibody on the development of bleomycin-induced pulmonary fibrosis

[161] The following example demonstrates the ability of a human anti-rat Timp-1 antibody (BW17.1) to prevent fibrotic collagen deposition in a bleomycin-induced rat lung fibrosis model.

[162] Male Lewis rats (6 weeks of age) received a single intratracheal challenge with bleomycin (0.3 mg/rat, in saline) or vehicle (saline) on day 0. Fourteen days later, animals were euthanized, the lung excised, fixed, and processed for evaluation of lung fibrosis. Lung tissue sections were cut, and quantitative assessment by image analysis of lung collagen in lung tissue sections stained with Mason Trichrome stain performed.

[163] Antibody administration: A 20 mg/kg dose of human ant-rat TIMP-1 antibody or control human antibody (IgG) was administered subcutaneously on day -1. Subsequently, a 10mg/kg dose of human ant-rat TIMP-1 antibody or control human antibody (IgG) was administered s.c. on days 2, 5, 8, and 11. The following five groups of animals were studied: Saline i.t. challenge + antibody vehicle (PBS); Saline i.t. challenge + TIMP-1 antibody; Bleomycin i.t. challenge + TIMP-1 antibody; Bleomycin i.t. challenge + antibody vehicle (PBS); Bleomycin i.t. challenge + control antibody.

[164] FIG. 14 shows the effect of the inhibitory effect of TIMP-1 antibody on bleomycin-induced lung fibrotic collagen.

EXAMPLE 24

Effect of BW-14 anti-TIMP-1 antibody in a rat model with CCl_4-induced liver fibrosis

[165] Carbon tetrachloride (CCl_4) was used to induce liver fibrosis as described in Example 9. A single intravenous dose of 3 mg/kg BW-14 or control antibody BW-3, respectively,

was administered on day 19. At this time, total liver collagen (hydroxyproline determined according to Prockop and Udenfried) is already significantly increased by CCl_4, and fibrotic collagen rapidly accumulates during the following weeks. The rats were sacrificed on day 28. The treatment groups were: no CCl_4 + control antibody BW 3 (n=10 rats), CCl_4 + control antibody BW 3 (n=20 rats), and CCl_4 + BW 14 (n=20 rats).

[166] The effect of control vs. TIMP-1 antibody as reflected in morphometric measurements of fibrous collagen (Sirius Red stained area as percentage of the total field) is shown in FIG. 15. Comparison of both control antibody treated groups shows that CCl_4 caused an approximately three-fold increase in collagen area. BW-14 antibody treatment reduced the pathological collagen increment by 26%. The lower fibrous collagen value of the CCl_4 + BW-14 group compared to the CCl_4 + BW-3 group was statistically significant ($p < 0.05$, Kolmogorow-Smirnow test).

REFERENCES

[167] Ausubel *et al.* (1998) Current Protocols in Molecular Biology. Wiley, New York, USA.

[168] Better *et al.*, (1988) Escherichia coli secretion of an active chimeric antibody fragment. Science 240, 1041.

[169] Bruggeman *et al.*, (1996) Phage antibodies against an unstable hapten: oxygen sensitive reduced flavin. FEBS Lett. 388, 242.

[170] Butler *et al.*, (1999) Human tissue inhibitor of metalloproteinases 3 interacts with both the N- and C-terminal domains of gelatinases A and B. Regulation by polyanions. J Biol Chem. 274, 10846.

[171] Gomis-Ruth *et al.*, (1996). Mechanism of inhibition of the human matrix metalloproteinase stromelysin-1 by TIMP-1. Nature. 389, 77.

[172] Griffiths, A.D. and Duncan, A.R. (1998) Strategies for selection of antibodies by phage display. Curr. Opin. Biotechnol. 9, 102.

[173] Hoogenboom, H.R. and Winter, G. (1992). By-passing immunisation. Human antibodies from synthetic repertoires of germline VH gene segments rearranged *in vitro*. J. Mol. Biol. 227, 381.

[174] Iredale *et al.*, (1996) Tissue inhibitor of metalloproteinase-1 messenger RNA expression is enhanced relative to interstitial collagenase messenger RNA in experimental liver injury and fibrosis. Hepatology. 24, 176.

[175] Knappik *et al.*, (2000) Fully synthetic human combinatorial antibody libraries (HuCAL) based on modular consensus frameworks and CDRs diversified with trinucleotides. J. Mol. Biol. 296, 55.

[176] Krebs *et al.*, (2001) High-throughput generation and engineering of recombinant human antibodies. J Immunol Methods. 254, 67.

[177] Lowman, H.B. (1997) Bacteriophage display and discovery of peptide leads for drug development. Annu. Rev. Biophys. Biomol. Struct. 26, 401.

[178] McCafferty *et al.*, (1990) Phage antibodies: filamentous phage displaying antibody variable domains. Nature 348, 552.

[179] Meng *et al.*, (1999) Residue 2 of TIMP-1 is a major determinant of affinity and specificity for matrix metalloproteinases but effects of substitutions do not correlate with those of the corresponding P1' residue of substrate. J Biol Chem. 274, 10184.

[180] Meulemans *et al.*, (1994) Selection of phage-displayed antibodies specific for a cytoskeletal antigen by competitive elution with a monoclonal antibody. J. Mol. Biol. 244, 353.

[181] Miyazaki *et al.*, (1999) Changes in the specificity of antibodies by site-specific mutagenesis followed by random mutagenesis. Protein Eng. 12, 407.

[182] Sheets *et al.*, (1998) Efficient construction of a large nonimmune phage antibody library: The production of high-affinity human single-chain antibodies to protein antigens. Proc. Natl. Acad. Sci. U.S.A. 95, 6157.

[183] Skerra, A. and Plückthun, A. (1988) Assembly of a functional immunoglobulin Fv fragment in Escherichia coli. Science 240, 1038.

[184] Smith, G.P. (1985) Filamentous fusion phage: novel expression vectors that display cloned antigens on the virion surface. Science 228, 1315.

[185] Smith, G.P. and Petrenko, V.A. (1997) Phage display. Chem. Rev. 97, 391.

[186] Stausbøl-Grøn *et al.*(1996) A model phage display subtraction method with potential for analysis of differential gene expression. FEBS Lett. 391, 71.

[187] Virnekäs *et al.* (1994) Trinucleotide phosphoramidites: ideal reagents for the synthesis of mixed oligonucleotides for random mutagenesis. Nucl. Acids Rès. 22, 5600.

CLAIMS

1. A purified preparation of a human antibody, wherein the antibody:

binds to a tissue inhibitor of metalloprotease-1 (TIMP-1); and

neutralizes a matrix metalloprotease (MMP)-inhibiting activity of the TIMP-1.

2. The preparation of claim 1 wherein the MMP is human MMP-1.

3. The preparation of claim 2 wherein the MMP is rat MMP-13.

4. The preparation of claim 1 wherein the TIMP-1 is a human TIMP-1.

5. The preparation of claim 4 wherein the antibody binds to the human TIMP-1 with a K_d selected from the group consisting of about 0.1 nM to about 10 μM, about 2 nM to about 1 μM, about 2 nM to about 200 nM, about 2 nM to about 150 nM, about 50 nM to about 100 nM, about 0.2 nM to about 13 nM, about 0.2 nM to about 0.5 nM, about 2 nM to about 13 nM, and about 0.5 nM to about 2 nM.

6. The preparation of claim 4 wherein the antibody binds to the human TIMP-1 with a K_d selected from the group consisting of about 0.2 nM, about 0.3 nM, about 0.5 M, about 0.6 nM, about 2 nM, about 7 nM, about 10 nM, about 11 nM, and about 13 nM.

7. The preparation of claim 4 wherein the antibody neutralizes the MMP-inhibiting activity of the human TIMP-1 with an IC_{50} selected from the group consisting of about .1 nM to about 200 nM, about 1 nM to about 100 nM, about 2 nM to about 50 nM, about 5 nM to about 25 nM, about 10 nM to about 15 nM, about 0.2 nM to about 11 nM, about 0.2 nM to about 4 nM, and about 4 nM to about 11 nM.

8. The preparation of claim 4 wherein the antibody neutralizes the MMP-inhibiting activity of the human TIMP-1 with an IC_{50} selected from the group consisting of about 0.2 nM, about 0.3 nM, about 0.4 nM, about 4 nM, about 7 nM, about 9 nM, and about 11 nM.

9. The preparation of claim 4 wherein the K_d for binding to human TIMP-1 and the IC_{50} for neutralizing the MMP-inhibiting activity of the human TIMP-1 are approximately equal.

10. The preparation of claim 1 wherein the TIMP-1 is a rat TIMP-1.

11. The preparation of claim 10 wherein the antibody binds to the rat TIMP-1 with a K_d selected from the group consisting of about 0.1 nM to about 10 μM, about 2 nM to about 1 μM, about 2 nM to about 200 nM, about 2 nM to about 150 nM, about 50 nM to about 100 nM, about 1.3 nM to about 13 nM, about 1.8 nM to about 10 nM, about 2 nM to about 9 nM, about 1.3 nM to about 9 nM, and about 2 nM to about 10 nM.

12. The preparation of claim 10 wherein the antibody binds to the rat TIMP-1 with a K_d selected from the group consisting of about 0.8 nM, about 1 nM, about 1.3 nM, about 1.9 nM, about 2 nM, about 3 nM, about 9 nM, about 10 nM, about 13 nM, about 14 nM, and about 15 nM.

13. The preparation of claim 10 wherein the antibody neutralizes the rat TIMP-1 activity with an IC_{50} selected from the group consisting of about .1 nM to about 300 nM, about 1 nM to about 100 nM, about 2 nM to about 50 nM, about 5 nM to about 25 nM, about 10 nM to about 15 nM, about 1.1 nM to about 14 nM, about 1.6 nM to about 11 nM, about 3

nM to about 7 nM, about 1.1 nM to about 7 nM, about 1.1 nM to about 11 nM, about 3 nM to about 11 nM, and about 3 nM to about 14 nM.

14. The preparation of claim 10 wherein the antibody neutralizes the rat TIMP-1 activity with an IC_{50} selected from the group consisting of about 1.1 nM, about 1.6 nM, about 3 nM, about 7 nM, about 11 nM, about 14 nM, about 19 nM, about 20 nM, about 30 nM, and about 100 nM.

15. The preparation of claim 10 wherein the K_d for binding to rat TIMP-1 and the IC_{50} for neutralizing the MMP-inhibiting activity of the rat TIMP-1 are approximately equal.

16. A purified preparation of a human antibody which comprises a VHCDR3 region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360.

17. A purified preparation of a human antibody which comprises a VLCDR3 region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379.

18. A purified preparation of a human antibody which comprises a VHCDR3 and VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NO:3 and 46, SEQ ID NOS:4 and 47, SEQ ID NOS:5 and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:8 and 51, SEQ ID NOS:9 and 52, SEQ ID NOS:10

and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ ID NOS:26 and 69, SEQ ID NOS: 27 and 70, SEQ ID NOS:28 and 71, SEQ ID NOS:29 and 72, SEQ ID NOS:30 and 73, SEQ ID NOS:31 and 74, SEQ ID NOS:32 and 75, SEQ ID NOS:33 and 76, SEQ ID NOS:34 and 77, SEQ ID NOS:35 and 78, SEQ ID NOS:36 and 79, SEQ ID NOS:37 and 80, SEQ ID NOS:38 and 81, SEQ ID NOS:39 and 82, SEQ ID NOS:40 and 83, SEQ ID NOS:41 and 84, SEQ ID NOS:42 and 85, SEQ ID NOS:43 and 86, SEQ ID NOS:3 and 48, SEQ ID NOS:360 and 48, SEQ ID NOS:3 and 365, SEQ ID NOS:16 and 59, SEQ ID NOS:18 and 61, SEQ ID NOS:34 and 77, SEQ ID NOS:34 and 379, SEQ ID NOS:18 and 376, SEQ ID NOS:18 and 377, and SEQ ID NOS:18 and 378.

19. A purified preparation of a human antibody comprising a VHCDR3 and VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NO:3 and 46, SEQ ID NOS:4 and 47, SEQ ID NOS:5 and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:8 and 51, SEQ ID NOS:9 and 52, SEQ ID NOS:10 and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID

NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ ID NOS:26 and 69, SEQ ID NOS: 27 and 70, SEQ ID NOS:28 and 71, SEQ ID NOS:29 and 72, SEQ ID NOS:30 and 73, SEQ ID NOS:31 and 74, SEQ ID NOS:32 and 75, SEQ ID NOS:33 and 76, SEQ ID NOS:34 and 77, SEQ ID NOS:35 and 78, SEQ ID NOS:36 and 79, SEQ ID NOS:37 and 80, SEQ ID NOS:38 and 81, SEQ ID NOS:39 and 82, SEQ ID NOS:40 and 83, SEQ ID NOS:41 and 84, SEQ ID NOS:42 and 85, SEQ ID NOS:43 and 86, SEQ ID NOS:3 and 48, SEQ ID NOS:360 and 48, SEQ ID NOS:3 and 365, SEQ ID NOS:16 and 59, SEQ ID NOS:18 and 61, SEQ ID NOS:34 and 77, SEQ ID NOS:34 and 379, SEQ ID NOS:18 and 376, SEQ ID NOS:18 and 377, and SEQ ID NOS:18 and 378.

20. The purified preparation of claim 19 wherein the human antibody comprises a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:140-182.

21. The purified preparation of claim 19 wherein the human antibody comprises a light chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:97-139.

22. A purified preparation of a human antibody which comprises a heavy chain and a light chain amino acid pair selected from the group consisting of SEQ ID NOS:140 and 97, SEQ ID NOS:141 and 98, SEQ ID NOS:142 and 99, SEQ ID NOS:143 and 100, SEQ ID NOS:144 and 101, SEQ ID NOS:145 and 102, SEQ ID NOS:146 and 103, SEQ ID NOS:142 and 97, SEQ ID NOS:142 and 98, SEQ ID NOS:142 and 100, SEQ ID NOS:142 and 101,

SEQ ID NOS:142 and 102, SEQ ID NOS:142 and 103, SEQ ID NOS:146 and 97, SEQ ID NOS:146 and 98, SEQ ID NO:146 and 100, SEQ ID NOS:146 and 101, SEQ ID NOS:148 and 104, SEQ ID NOS:148 and 105, SEQ ID NOS:149 and 106, SEQ ID NOS:150 and 107, SEQ ID NOS:151 and 108, SEQ ID NOS:152 and 109, SEQ ID NOS:153 and 110, SEQ ID NOS:154 and 111, SEQ ID NOS:155 and 112, SEQ ID NOS:156 and 113, SEQ ID NOS:157 and 114, SEQ ID NOS:158 and 115, SEQ ID NOS:159 and 116, SEQ ID NOS:160 and 117, SEQ ID NOS:161 and 118, SEQ ID NOS:162 and 119, SEQ ID NOS:163 and 120, SEQ ID NOS:164 and 121, SEQ ID NOS:165 and 122, SEQ ID NOS:166 and 123, SEQ ID NOS:167 and 124, SEQ ID NOS:168 and 125, SEQ ID NOS:169 and 126, SEQ ID NOS:170 and 127, SEQ ID NOS:171 and 128, SEQ ID NOS:172 and 129, SEQ ID NOS:173 and 130, SEQ ID NOS:174 and 131, SEQ ID NOS:175 and 132, SEQ ID NOS:176 and 133, SEQ ID NOS:177 and 134, SEQ ID NOS:178 and 135, SEQ ID NOS:179 and 136, SEQ ID NOS:180 and 137, SEQ ID NOS:181 and 138, and SEQ ID NOS:182 and 139.

23. A pharmaceutical composition comprising:

a human antibody which (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1; and

a pharmaceutically acceptable carrier.

24. The pharmaceutical composition of claim 23 wherein the MMP is human MMP-1.

25. The pharmaceutical composition of claim 23 wherein the MMP is rat MMP-13.

26. The pharmaceutical composition of claim 23 wherein the TIMP-1 is a human TIMP-1.

27. The pharmaceutical composition of claim 23 wherein the TIMP-1 is a rat TIMP-1.

28. The pharmaceutical composition of claim 23 wherein a K_d for binding to the TIMP-1 and an IC_{50} for neutralizing the MMP-1-inhibiting activity of the TIMP-1 are approximately equal.

29. A purified polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360, wherein the human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.

30. The purified polynucleotide of claim 31 wherein the VHCDR3 region is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:227-269.

31. A purified polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379, wherein the human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.

32. The purified polynucleotide of claim 31 wherein the VLCDR3 region is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:184-226.

33. The purified polynucleotide of claim 31 wherein the human antibody comprises a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:140-182.

34. The purified polynucleotide of claim 33 wherein the heavy chain is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:269-311.

35. The purified polynucleotide of claim 33 wherein the human antibody comprises a light chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:97-139.

36. The purified polynucleotide of claim 35 wherein the light chain is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:312-354.

37. An expression vector comprising the polynucleotide of claim 29.

38. An expression vector comprising the polynucleotide of claim 30.

39. An expression vector comprising the polynucleotide of claim 31.

40. An expression vector comprising the polynucleotide of claim 32.

41. An expression vector comprising the polynucleotide of claim 33.

42. An expression vector comprising the polynucleotide of claim 34.

43. An expression vector comprising the polynucleotide of claim 35.

44. An expression vector comprising the polynucleotide of claim 36.

45. A host cell comprising the expression vector of claim 37.

46. A host cell comprising the expression vector of claim 38.

47. A host cell comprising the expression vector of claim 39.

48. A host cell comprising the expression vector of claim 40.

49. A host cell comprising the expression vector of claim 41.

50. A host cell comprising the expression vector of claim 42.

51. A host cell comprising the expression vector of claim 43.

52. A host cell comprising the expression vector of claim 44.

53. A method of making a human antibody, comprising the steps of:

culturing the host cell of claim 45 under conditions whereby the antibody is expressed; and

purifying the human antibody from the host cell culture.

54. The method of claim 55 wherein the expression vector comprises a polynucleotide sequence selected from the group consisting of SEQ ID NOS:183-357.

55. A method of decreasing an MMP-inhibiting activity of a TIMP-1, comprising the step of:

contacting the TIMP-1 with a human antibody that binds to the TIMP-1, whereby the MMP-inhibiting activity of the TIMP-1 is decreased relative to MMP-inhibiting activity of the TIMP-1 in the absence of the antibody.

56. The method of claim 55 wherein the MMP is human MMP-1.

57. The method of claim 55 wherein the MMP is rat MMP-13.

58. The method of claim 55 wherein the TIMP-1 is a human TIMP-1.

59. The method of claim 55 wherein the TIMP-1 is a rat TIMP-1.

60. The method of claim 55 wherein the step of contacting is carried out in a cell-free system.

61. The method of claim 55 wherein the step of contacting is carried out in a cell culture system.

62. The method of claim 55 wherein the step of contacting is carried out *in vivo*.

63. The method of claim 55 wherein the antibody comprises a VHCDR3 and a VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NO:3 and 46, SEQ ID NOS:4 and 47, SEQ ID NOS:5 and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:8 and 51, SEQ ID NOS:9 and 52, SEQ ID NOS:10 and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ ID NOS:26 and 69, SEQ ID NOS: 27 and 70, SEQ ID NOS:28 and 71, SEQ ID NOS:29 and 72, SEQ ID NOS:30 and 73, SEQ ID NOS:31 and 74, SEQ ID NOS:32 and 75, SEQ ID NOS:33 and 76, SEQ ID NOS:34 and 77, SEQ ID NOS:35 and 78, SEQ ID NOS:36 and 79, SEQ ID NOS:37 and 80, SEQ ID NOS:38 and 81, SEQ ID NOS:39 and 82, SEQ ID NOS:40 and 83, SEQ ID NOS:41 and 84, SEQ ID NOS:42 and 85, SEQ ID NOS:43 and 86, SEQ ID NOS:3 and 48, SEQ ID NOS:360 and 48, SEQ ID NOS:3 and 365, SEQ ID NOS:16 and 59, SEQ ID NOS:18 and 61, SEQ ID NOS:34 and 77, SEQ ID NOS:34 and 379, SEQ ID NOS:18 and 376, SEQ ID NOS:18 and 377, and SEQ ID NOS:18 and 378.

64. A method of ameliorating symptoms of a disorder in which TIMP-1 is elevated, comprising the step of:

administering to a patient having the disorder an effective amount of a human antibody which neutralizes an MMP-inhibiting activity of the TIMP-1, whereby symptoms of the disorder are ameliorated.

65. The method of claim 64 wherein the MMP is human MMP-1.

66. The method of claim 64 wherein the MMP is rat MMP-13.

67. The method of claim 64 wherein the disorder is selected from the group consisting of liver fibrosis, alcoholic liver disease, cardiac fibrosis, acute coronary syndrome, lupus nephritis, glomerulosclerotic renal disease, idiopathic pulmonary fibrosis, benign prostate hypertrophy, lung cancer, and colon cancer.

68. The method of claim 64 wherein the antibody comprises a VHCDR3 and a VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NO:3 and 46, SEQ ID NOS:4 and 47, SEQ ID NOS:5 and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:8 and 51, SEQ ID NOS:9 and 52, SEQ ID NOS:10 and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ ID NOS:26 and 69, SEQ ID NOS: 27 and 70, SEQ ID NOS:28 and 71,

SEQ ID NOS:29 and 72, SEQ ID NOS:30 and 73, SEQ ID NOS:31 and 74, SEQ ID NOS:32 and 75, SEQ ID NOS:33 and 76, SEQ ID NOS:34 and 77, SEQ ID NOS:35 and 78, SEQ ID NOS:36 and 79, SEQ ID NOS:37 and 80, SEQ ID NOS:38 and 81, SEQ ID NOS:39 and 82, SEQ ID NOS:40 and 83, SEQ ID NOS:41 and 84, SEQ ID NOS:42 and 85, SEQ ID NOS:43 and 86, SEQ ID NOS:3 and 48, SEQ ID NOS:360 and 48, SEQ ID NOS:3 and 365, SEQ ID NOS:16 and 59, SEQ ID NOS:18 and 61, SEQ ID NOS:34 and 77, SEQ ID NOS:34 and 379, SEQ ID NOS:18 and 376, SEQ ID NOS:18 and 377, and SEQ ID NOS:18 and 378.

69. A method of detecting a TIMP-1 in a test preparation, comprising the steps of:

contacting the test preparation with a human antibody that specifically binds to the TIMP-1; and

assaying the test preparation for the presence of an antibody-TIMP-1 complex.

70. The method of claim 69 wherein the antibody comprises a detectable label.

71. The method of claim 69 wherein the antibody is bound to a solid support.

72. The method of claim 69 wherein the antibody comprises a VHCDR3 and a VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NO:3 and 46, SEQ ID NOS:4 and 47, SEQ ID NOS:5 and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:8 and 51, SEQ ID NOS:9 and 52, SEQ ID NOS:10 and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID

NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ ID NOS:26 and 69, SEQ ID NOS: 27 and 70, SEQ ID NOS:28 and 71, SEQ ID NOS:29 and 72, SEQ ID NOS:30 and 73, SEQ ID NOS:31 and 74, SEQ ID NOS:32 and 75, SEQ ID NOS:33 and 76, SEQ ID NOS:34 and 77, SEQ ID NOS:35 and 78, SEQ ID NOS:36 and 79, SEQ ID NOS:37 and 80, SEQ ID NOS:38 and 81, SEQ ID NOS:39 and 82, SEQ ID NOS:40 and 83, SEQ ID NOS:41 and 84, SEQ ID NOS:42 and 85, and SEQ ID NOS:43 and 86.

73. A method to aid in diagnosing a disorder in which a TIMP-1 level is elevated, comprising the steps of:

contacting a sample from a patient suspected of having the disorder with a human antibody that binds to TIMP-1; and

assaying for the presence of an antibody-TIMP-1 complex, whereby detection of an amount of the complex which is greater than an amount of the complex in a normal sample identifies the patient as likely to have the disorder.

74. The method of claim 73 wherein the antibody comprises a detectable label.

75. The method of claim 73 wherein the antibody is bound to a solid support.

76. The method of claim 73 wherein the antibody comprises a VHCDR3 and a VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NO:3 and 46, SEQ ID NOS:4 and 47, SEQ ID

NOS:5 and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:8 and 51, SEQ ID NOS:9 and 52, SEQ ID NOS:10 and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ ID NOS:26 and 69, SEQ ID NOS: 27 and 70, SEQ ID NOS:28 and 71, SEQ ID NOS:29 and 72, SEQ ID NOS:30 and 73, SEQ ID NOS:31 and 74, SEQ ID NOS:32 and 75, SEQ ID NOS:33 and 76, SEQ ID NOS:34 and 77, SEQ ID NOS:35 and 78, SEQ ID NOS:36 and 79, SEQ ID NOS:37 and 80, SEQ ID NOS:38 and 81, SEQ ID NOS:39 and 82, SEQ ID NOS:40 and 83, SEQ ID NOS:41 and 84, SEQ ID NOS:42 and 85, SEQ ID NOS:43 and 86, SEQ ID NOS:3 and 48, SEQ ID NOS:360 and 48, SEQ ID NOS:3 and 365, SEQ ID NOS:16 and 59, SEQ ID NOS:18 and 61, SEQ ID NOS:34 and 77, SEQ ID NOS:34 and 379, SEQ ID NOS:18 and 376, SEQ ID NOS:18 and 377, and SEQ ID NOS:18 and 378.

77. The method of claim 73 wherein the sample is obtained from a tissue selected from the group consisting of colon, liver, heart, kidney, prostate, serum, and lung.

78. The method of claim 73 wherein the disorder is selected from the group consisting of liver fibrosis, alcoholic liver disease, cardiac fibrosis, acute cardiac syndrome,

lupus nephritis, glomerulosclerotic renal disease, benign prostate hypertrophy, lung cancer, colon cancer, and idiopathic pulmonary fibrosis.

Sequence Summary HuCAL Libraries scFv1, scFv2, scFv3 and Fab1

VL

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	a	b	c	d	e	f	31	32	33	34
	Framework 1																							CDR 1																
	EcoRV						BanII																PstI																	
VLκ1	D	I	Q	M	T	Q	S	P	S	S	L	S	A	S	V	G	D	R	V	T	I	T	C	R	A	S	Q	G	I	S	-	-	-	-	-	-	S	Y	L	A
VLκ2	D	I	V	M	T	Q	S	P	L	S	L	P	V	T	P	G	E	P	A	S	I	S	C	R	S	S	Q	S	L	L	H	S	-	N	G	Y	N	Y	L	D
VLκ3	D	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T	L	S	C	R	A	S	Q	S	V	S	S	-	-	-	-	-	S	Y	L	A
VLκ4	D	I	V	M	T	Q	S	P	D	S	L	A	V	S	L	G	E	R	A	T	I	N	C	R	S	S	Q	S	V	L	Y	S	S	N	N	K	N	Y	L	A
VLλ1	D	I	V	L	T	Q	P	P	-	S	V	S	G	A	P	G	Q	R	V	T	I	S	C	S	G	S	S	S	N	I	G	S	-	-	-	-	N	Y	V	S
VLλ2	D	I	A	L	T	Q	P	A	-	S	V	S	G	S	P	G	Q	S	I	T	I	S	C	T	G	T	S	S	D	V	G	G	Y	-	-	-	N	Y	V	S
VLλ3	D	I	E	L	T	Q	P	P	-	S	V	S	V	A	P	G	Q	T	A	R	I	S	C	S	G	D	A	L	G	D	-	-	-	-	-	-	K	Y	A	S
	EcoRV														SexAI							BssSI																		

VH

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	a	b	32	33	34	35	36	37	38
	Framework 1																									CDR 1														
			MfeI																						BspEI															
VH1A	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	S	S	V	K	V	S	C	K	A	S	G	G	T	F	S	S	-	-	Y	A	I	S	W	V	R
VH1B	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	A	S	V	K	V	S	C	K	A	S	G	Y	T	F	T	S	-	-	Y	Y	M	H	W	V	R
VH2	Q	V	Q	L	K	E	S	G	P	A	L	V	K	P	T	Q	T	L	T	L	T	C	T	F	S	G	F	S	L	S	T	S	G	V	G	V	G	W	I	R
VH3	Q	V	Q	L	V	E	S	G	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	A	S	G	F	T	F	S	S	-	-	Y	A	M	S	W	V	R
VH4	Q	V	Q	L	Q	E	S	G	P	G	L	V	K	P	S	E	T	L	S	L	T	C	T	V	S	G	G	S	I	S	S	-	-	Y	Y	W	S	W	I	R
VH5	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	E	S	L	K	I	S	C	K	G	S	G	Y	S	F	T	S	-	-	Y	W	I	G	W	V	R
VH6	Q	V	Q	L	Q	Q	S	G	P	G	L	V	K	P	S	Q	T	L	S	L	T	C	A	I	S	G	D	S	V	S	S	N	S	A	A	W	N	W	I	R

FIG. 1

Framework 2 | CDR 2 | Framework 3

					4										5										6										7									
5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9
KpnI					SexAI							AseI											SanDI								BamHI													
W	Y	Q	Q	K	P	G	K	A	P	K	L	L	I	Y	A	A	S	S	L	Q	S	G	V	P	S	R	F	S	G	S	G	S	G	T	D	F	T	L	T	I	S	S	L	Q
W	Y	L	Q	K	P	G	Q	S	P	Q	L	L	I	Y	L	G	S	N	R	A	S	G	V	P	D	R	F	S	G	S	G	S	G	T	D	F	T	L	K	I	S	R	V	E
W	Y	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	G	A	S	S	R	A	T	G	V	P	A	R	F	S	G	S	G	S	G	T	D	F	T	L	T	I	S	S	L	E
W	Y	Q	Q	K	P	G	Q	P	P	K	L	L	I	Y	W	A	S	T	R	E	S	G	V	P	D	R	F	S	G	S	G	S	G	T	D	F	T	L	T	I	S	S	L	Q
W	Y	Q	Q	L	P	G	T	A	P	K	L	L	I	Y	D	N	N	Q	R	P	S	G	V	P	D	R	F	S	G	S	K	S	G	T	S	A	S	L	A	I	T	G	L	Q
W	Y	Q	Q	H	P	G	K	A	P	K	L	M	I	Y	D	V	S	N	R	P	S	G	V	S	N	R	F	S	G	S	K	S	G	N	T	A	S	L	T	I	S	G	L	Q
W	Y	Q	Q	K	P	G	Q	A	P	V	L	V	I	Y	D	D	S	D	R	P	S	G	I	P	E	R	F	S	G	S	N	S	G	N	T	A	T	L	T	I	S	G	T	Q
KpnI					XmaI			BbeI												Bsu36I									BamHI															

Framework 2 | CDR 2 | Fra

	4										5													6										7										8
9	0	1	2	3	4	5	6	7	8	9	0	1	2	a	b	c	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0
	BstXI					XhoI																									BstEII							NspV						
Q	A	P	G	Q	G	L	E	W	M	G	G	I	I	P	-	-	I	F	G	T	A	N	Y	A	Q	K	F	Q	G	R	V	T	I	T	A	D	E	S	T	S	T	A	Y	M
Q	A	P	G	Q	G	L	E	W	M	G	W	I	N	P	-	-	N	S	G	G	T	N	Y	A	Q	K	F	Q	G	R	V	T	M	T	R	D	T	S	I	S	T	A	Y	M
Q	P	P	G	K	A	L	E	W	L	A	L	I	D	-	-	-	W	D	D	D	K	Y	Y	S	T	S	L	K	T	R	L	T	I	S	K	D	T	S	K	N	Q	V	V	L
Q	A	P	G	K	G	L	E	W	V	S	A	I	S	G	-	-	S	G	G	S	T	Y	Y	A	D	S	V	K	G	R	F	T	I	S	R	D	N	S	K	N	T	L	Y	L
Q	P	P	G	K	G	L	E	W	I	G	Y	I	Y	-	-	-	Y	S	G	S	T	N	Y	N	P	S	L	K	S	R	V	T	I	S	V	D	T	S	K	N	Q	F	S	L
Q	M	P	G	K	G	L	E	W	M	G	I	I	Y	P	-	-	G	D	S	D	T	R	Y	S	P	S	F	Q	G	Q	V	T	I	S	A	D	K	S	I	S	T	A	Y	L
Q	S	P	G	R	G	L	E	W	L	G	R	T	Y	Y	R	-	S	K	W	Y	N	D	Y	A	V	S	V	K	S	R	I	T	I	N	P	D	T	S	K	N	Q	F	S	L

FIG. 1, Cont.

CDR 3 | Framework 4

8										9												10									
0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	a	b	6	7	8	9	0	1	2	3	4	5	6	7	8	9
	BbsI																				MscI									BsiWI	
P	E	D	F	A	T/V	Y	Y	C	X	Q	X	X	X	X	X	-	-	X	T	F	G	Q	G	T	K	V	E	I	K	R	T
A	E	D	V	G	V	Y	Y	C	X	Q	X	X	X	X	X	-	-	X	T	F	G	Q	G	T	K	V	E	I	K	R	T
P	E	D	F	A	T/V	Y	Y	C	X	Q	X	X	X	X	X	-	-	X	T	F	G	Q	G	T	K	V	E	I	K	R	T
A	E	D	V	A	V	Y	Y	C	X	Q	X	X	X	X	X	-	-	X	T	F	G	Q	G	T	K	V	E	I	K	R	T
S	E	D	E	A	D	Y	Y	C	Q	S	X	D	X	X	X	(X)	(X)	X	V	F	G	G	G	T	K	L	T	V	L	G	
A	E	D	E	A	D	Y	Y	C	Q	S	X	D	X	X	X	(X)	(X)	X	V	F	G	G	G	T	K	L	T	V	L	G	
A	E	D	E	A	D	Y	Y	C	Q	S	X	D	X	X	X	(X)	(X)	X	V	F	G	G	G	T	K	L	T	V	L	G	
	BbsI																									HpaI				MscI	

mework 3 | CDR 3 | Framework 4

												9										10																				11			
1	2	a	b	c	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	a	b	c	d	e	f	g	h	i	j	1	2	3	4	5	6	7	8	9	0	1	2	3
										EagI				BssHII																							StyI							BlpI	
E	L	S	S	L	R	S	E	D	T	A	V	Y	Y	C	A	R	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	X	X	D	X	W	G	Q	G	T	L	V	T	V	S	S
E	L	S	S	L	R	S	E	D	T	A	V	Y	Y	C	A	R	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	X	X	D	X	W	G	Q	G	T	L	V	T	V	S	S
T	M	T	N	M	D	P	V	D	T	A	T	Y	Y	C	A	R	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	X	X	D	X	W	G	Q	G	T	L	V	T	V	S	S
Q	M	N	S	L	R	A	E	D	T	A	V	Y	Y	C	A	R	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	X	X	D	X	W	G	Q	G	T	L	V	T	V	S	S
K	L	S	S	V	T	A	A	D	T	A	V	Y	Y	C	A	R	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	X	X	D	X	W	G	Q	G	T	L	V	T	V	S	S
Q	W	S	S	L	K	A	S	D	T	A	M	Y	Y	C	A	R	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	X	X	D	X	W	G	Q	G	T	L	V	T	V	S	S
Q	L	N	S	V	T	P	E	D	T	A	V	Y	Y	C	A	R	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	X	X	D	X	W	G	Q	G	T	L	V	T	V	S	S

FIG. 1, cont.

Sequence Summary HuCAL Libraries scFv1, scFv2, scFv3 and Fab1

VL

Framework 1 (positions 1–23) | CDR 1 (positions 24–34)

Position	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	a	b	c	d	e	f	31	32	33	34	35	36	37	38
	EcoRV						BanII																PstI																			KpnI		
VLκ1	GAT	ATC	CAG	ATG	ACC	CAG	AGC	CCG	TCT	AGC	CTG	AGC	GCG	AGC	GTG	GGT	GAT	CGT	GTG	ACC	ATT	ACC	TGC	AGA	GCG	AGC	CAG	GGC	ATT	AGC	AGC	---	---	---	---	---	---	TAT	CTG	GCG	TGG	TAC	CAG	CAG
VLκ2	GAT	ATC	GTG	ATG	ACC	CAG	AGC	CCA	CTG	AGC	CTG	CCA	GTG	ACT	CCG	GGC	GAG	CCT	GCG	AGC	ATT	AGC	TGC	AGA	AGC	AGC	CAA	AGC	CTG	CTG	CAT	AGC	---	AAC	GGC	TAT	AAC	TAT	CTG	GAT	TGG	TAC	CTT	CAA
VLκ3	GAT	ATC	GTG	CTG	ACC	CAG	AGC	CCG	GCG	ACC	CTG	AGC	CTG	TCT	CCG	GGC	GAA	CGT	GCG	ACC	CTG	AGC	TGC	AGA	GCG	AGC	CAG	AGC	GTG	AGC	AGC	---	---	---	---	---	AGC	TAT	CTG	GCG	TGG	TAC	CAG	CAG
VLκ4	GAT	ATC	GTG	ATG	ACC	CAG	AGC	CCG	GAT	AGC	CTG	GCG	GTG	AGC	CTG	GGC	GAA	CGT	GCG	ACC	ATT	AAC	TGC	AGA	AGC	AGC	CAG	AGC	GTG	CTG	TAT	AGC	AGC	AAC	AAC	AAA	AAC	TAT	CTG	GCG	TGG	TAC	CAG	CAG
VLλ1	GAT	ATC	GTG	CTG	ACC	CAG	CCG	CCT	.	TCA	GTG	AGT	GGC	GCA	CCA	GGT	CAG	CGT	GTG	ACC	ATC	TCG	TGT	AGC	GGC	AGC	AGC	AGC	AAC	ATT	GGC	AGC	AAC	---	---	---	---	TAT	GTG	AGC	TGG	TAC	CAG	CAG
VLλ2	GAT	ATC	GCA	CTG	ACC	CAG	CCA	GCT	.	TCA	GTG	AGC	GGC	TCA	CCA	GGT	CAG	AGC	ATT	ACC	ATC	TCG	TGT	ACG	GGT	ACT	AGC	AGC	GAT	GTG	GGC	GGC	TAT	AAC	---	---	---	TAT	GTG	AGC	TGG	TAC	CAG	CAG
VLλ3	GAT	ATC	GAA	CTG	ACC	CAG	CCG	CCT	.	TCA	GTG	AGC	GTT	GCA	CCA	GGT	CAG	ACC	GCG	CGT	ATC	TCG	TGT	AGC	GGC	---	GAT	GCG	---	CTG	GGC	GAT	AAA	---	---	---	---	TAC	GCG	AGC	TGG	TAC	CAG	CAG
	EcoRV														SexAI							BssSI																				KpnI		

VH

Framework 1 (positions 1–26) | CDR 1 (positions 27–35) | Frame...

Position	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	a	b	32	33	34	35	36	37	38	39	40	41	42
			MfeI																						BspEI																BstXI			
VH1A	CAG	GTG	CAA	TTG	GTT	CAG	TCT	GGC	GCG	GAA	GTG	AAA	AAA	CCG	GGC	AGC	AGC	GTG	AAA	GTG	AGC	TGC	AAA	GCC	TCC	GGA	GGC	ACT	TTT	AGC	AGC	-	-	TAT	GCG	ATT	AGC	TGG	GTG	CGC	CAA	GCC	CCT	GGG
VH1B	CAG	GTG	CAA	TTG	GTT	CAG	AGC	GGC	GCG	GAA	GTG	AAA	AAA	CCG	GGC	GCG	AGC	GTG	AAA	GTG	AGC	TGC	AAA	GCC	TCC	GGA	TAT	ACC	TTT	ACC	AGC	-	-	TAT	TAT	ATG	CAC	TGG	GTC	CGC	CAA	GCC	CCT	GGG
VH2	CAG	GTG	CAA	TTG	AAA	GAA	AGC	GGC	CCG	GCC	CTG	GTG	AAA	CCG	ACC	CAA	ACC	CTG	ACC	CTG	ACC	TGT	ACC	TTT	TCC	GGA	TTT	AGC	CTG	TCC	ACG	TCT	GGC	GTT	GGC	GTG	GGC	TGG	ATT	CGC	CAG	CCG	CCT	GGG
VH3	CAG	GTG	CAA	TTG	GTG	GAA	AGC	GGC	GGC	GGC	CTG	GTG	CAA	CCG	GGC	GGC	AGC	CTG	CGT	CTG	AGC	TGC	GCG	GCC	TCC	GGA	TTT	ACC	TTT	AGC	AGC	-	-	TAT	GCG	ATG	AGC	TGG	GTG	CGC	CAA	GCC	CCT	GGG
VH4	CAG	GTG	CAA	TTG	CAA	GAA	AGT	GGT	CCG	GGC	CTG	GTG	AAA	CCG	AGC	GAA	ACC	CTG	AGC	CTG	ACC	TGC	ACC	GTT	TCC	GGA	GGC	AGC	ATT	AGC	AGC	-	-	TAT	TAT	TGG	AGC	TGG	ATT	CGC	CAG	CCG	CCT	GGG
VH5	CAG	GTG	CAA	TTG	GTT	CAG	AGC	GGC	GCG	GAA	GTG	AAA	AAA	CCG	GGC	GAA	AGC	CTG	AAA	ATT	AGC	TGC	AAA	GGT	TCC	GGA	TAT	TCC	TTT	ACG	AGC	-	-	TAT	TGG	ATT	GGC	TGG	GTG	CGC	CAG	ATG	CCT	GGG
VH6	CAG	GTG	CAA	TTG	CAA	CAG	TCT	GGT	CCG	GGC	CTG	GTG	AAA	CCG	AGC	CAA	ACC	CTG	AGC	CTG	ACC	TGT	GCG	ATT	TCC	GGA	GAT	AGC	GTG	AGC	AGC	AAC	AGC	GCG	GCG	TGG	AAC	TGG	ATT	CGC	CAG	TCT	CCT	GGG

FIG. 2

Framework 2 (positions 39–49) · CDR 2 (positions 50–56) · Framework 3 (positions 57–84)

Restriction sites (rows 1–4): SexAI, AseI, SanDI, BamHI, BbsI. Restriction sites (rows 5–7): XmaI, BbeI, Bsu36I, BamHI, BbsI.

39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84
AAA	CCA	GGT	AAA	GCA	CCG	AAA	CTA	TTA	ATT	TAT	GCA	GCC	AGC	AGC	TTG	CAA	AGC	GGG	GTC	CCG	TCC	CGT	TTT	AGC	GGC	TCT	GGA	TCC	GGC	ACT	GAT	TTT	ACC	CTG	ACC	ATT	AGC	AGC	CTG	CAA	CCT	GAA	GAC	TTT	GCG
AAA	CCA	GGT	CAA	AGC	CCG	CAG	CTA	TTA	ATT	TAT	CTG	GGC	AGC	AAC	CGT	GCC	AGT	GGG	GTC	CCG	GAT	CGT	TTT	AGC	GGC	TCT	GGA	TCC	GGC	ACC	GAT	TTT	ACC	CTG	AAA	ATT	AGC	CGT	GTG	GAA	GCT	GAA	GAC	GTG	GGC
AAA	CCA	GGT	CAA	GCA	CCG	CGT	CTA	TTA	ATT	TAT	GGC	GCG	AGC	AGC	CGT	GCA	ACT	GGG	GTC	CCG	GCG	CGT	TTT	AGC	GGC	TCT	GGA	TCC	GGC	ACG	GAT	TTT	ACC	CTG	ACC	ATT	AGC	AGC	CTG	GAA	CCT	GAA	GAC	TTT	GCG
AAA	CCA	GGT	CAG	CCG	CCG	AAA	CTA	TTA	ATT	TAT	TGG	GCA	TCC	ACC	CGT	GAA	AGC	GGG	GTC	CCG	GAT	CGT	TTT	AGC	GGC	TCT	GGA	TCC	GGC	ACT	GAT	TTT	ACC	CTG	ACC	ATT	TCG	TCC	CTG	CAA	GCT	GAA	GAC	GTG	GCG
TTG	CCC	GGG	ACG	GCG	CCG	AAA	CTG	CTG	ATT	TAT	GAT	AAC	AAC	CAG	CGT	CCC	TCA	GGC	GTG	CCG	GAT	CGT	TTT	AGC	GGA	TCC	AAA	AGC	GGC	ACC	AGC	GCG	AGC	CTT	GCG	ATT	ACG	GGC	CTG	CAA	AGC	GAA	GAC	GAA	GCG
CAT	CCC	GGG	AAG	GCG	CCG	AAA	CTG	ATG	ATT	TAT	GAT	GTG	AGC	AAC	CGT	CCC	TCA	GGC	GTG	AGC	AAC	CGT	TTT	AGC	GGA	TCC	AAA	AGC	GGC	AAC	ACC	GCG	AGC	CTG	ACC	ATT	AGC	GGC	CTG	CAA	GCG	GAA	GAC	GAA	GCG
AAA	CCC	GGG	CAG	GCG	CCA	GTT	CTG	GTG	ATT	TAT	GAT	GAT	TCT	GAC	CGT	CCC	TCA	GGC	ATC	CCG	GAA	CGC	TTT	AGC	GGA	TCC	AAC	AGC	GGC	AAC	ACC	GCG	ACC	CTG	ACC	ATT	AGC	GGC	ACT	CAG	GCG	GAA	GAC	GAA	GCG

work 2 (positions 43–49) · CDR 2 (positions 50–65) · Framework 3 (positions 66–82c)

Restriction sites: XhoI, BstEII, NspV

43	44	45	46	47	48	49	50	51	52	a	b	c	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	a	b	c
CAG	GGT	CTC	GAG	TGG	ATG	GGC	GGC	ATT	ATT	CCG	-	-	ATT	TTT	GGC	ACG	GCG	AAC	TAC	GCG	CAG	AAG	TTT	CAG	GGC	CGG	GTG	ACC	ATT	ACC	GCG	GAT	GAA	AGC	ACC	AGC	ACC	GCG	TAT	ATG	GAA	CTG	AGC	AGC	CTG
CAG	GGT	CTC	GAG	TGG	ATG	GGC	TGG	ATT	AAC	CCG	-	-	AAT	AGC	GGC	GGC	ACG	AAC	TAC	GCG	CAG	AAG	TTT	CAG	GGC	CGG	GTG	ACC	ATG	ACC	CGT	GAT	ACC	AGC	ATT	AGC	ACC	GCG	TAT	ATG	GAA	CTG	AGC	AGC	CTG
AAA	GCC	CTC	GAG	TGG	CTG	GCT	CTG	ATT	GAT	-	-	-	TGG	GAT	GAT	GAT	AAG	TAT	TAT	AGC	ACC	AGC	CTG	AAA	ACG	CGT	CTG	ACC	ATT	AGC	AAA	GAT	ACT	TCG	AAA	AAT	CAG	GTG	GTG	CTG	ACT	ATG	ACC	AAC	ATG
AAG	GGT	CTC	GAG	TGG	GTG	AGC	GCG	ATT	AGC	GGT	-	-	AGC	GGC	GGC	AGC	ACC	TAT	TAT	GCG	GAT	AGC	GTG	AAA	GGC	CGT	TTT	ACC	ATT	TCA	CGT	GAT	AAT	TCG	AAA	AAC	ACC	CTG	TAT	CTG	CAA	ATG	AAC	AGC	CTG
AAG	GGT	CTC	GAG	TGG	ATT	GGC	TAT	ATT	TAT	-	-	-	TAT	AGC	GGC	AGC	ACC	AAG	TAT	AAT	CCG	AGC	CTG	AAA	AGC	CGG	GTG	ACC	ATT	AGC	GTT	GAT	ACT	TCG	AAA	AAC	CAG	TTT	AGC	CTG	AAA	CTG	AGC	AGC	GTG
AAG	GGT	CTC	GAG	TGG	ATG	GGC	ATT	ATT	TAT	CCG	-	-	GGC	GAT	AGC	GAT	ACC	CGT	TAT	TCT	CCG	AGC	TTT	CAG	GGC	CAG	GTG	ACC	ATT	AGC	GCG	GAT	AAA	AGC	ATT	AGC	ACC	GCG	TAT	CTT	CAA	TGG	AGC	AGC	CTG
CGT	GGC	CTC	GAG	TGG	CTG	GGC	CGT	ACC	TAT	TAT	CGT	-	AGC	AAA	TGG	TAT	AAC	GAT	TAT	GCG	GTG	AGC	GTG	AAA	AGC	CGG	ATT	ACC	ATC	AAC	CCG	GAT	ACT	TCG	AAA	AAC	CAG	TTT	AGC	CTG	CAA	CTG	AAC	AGC	GTG

FIG. 2, cont.

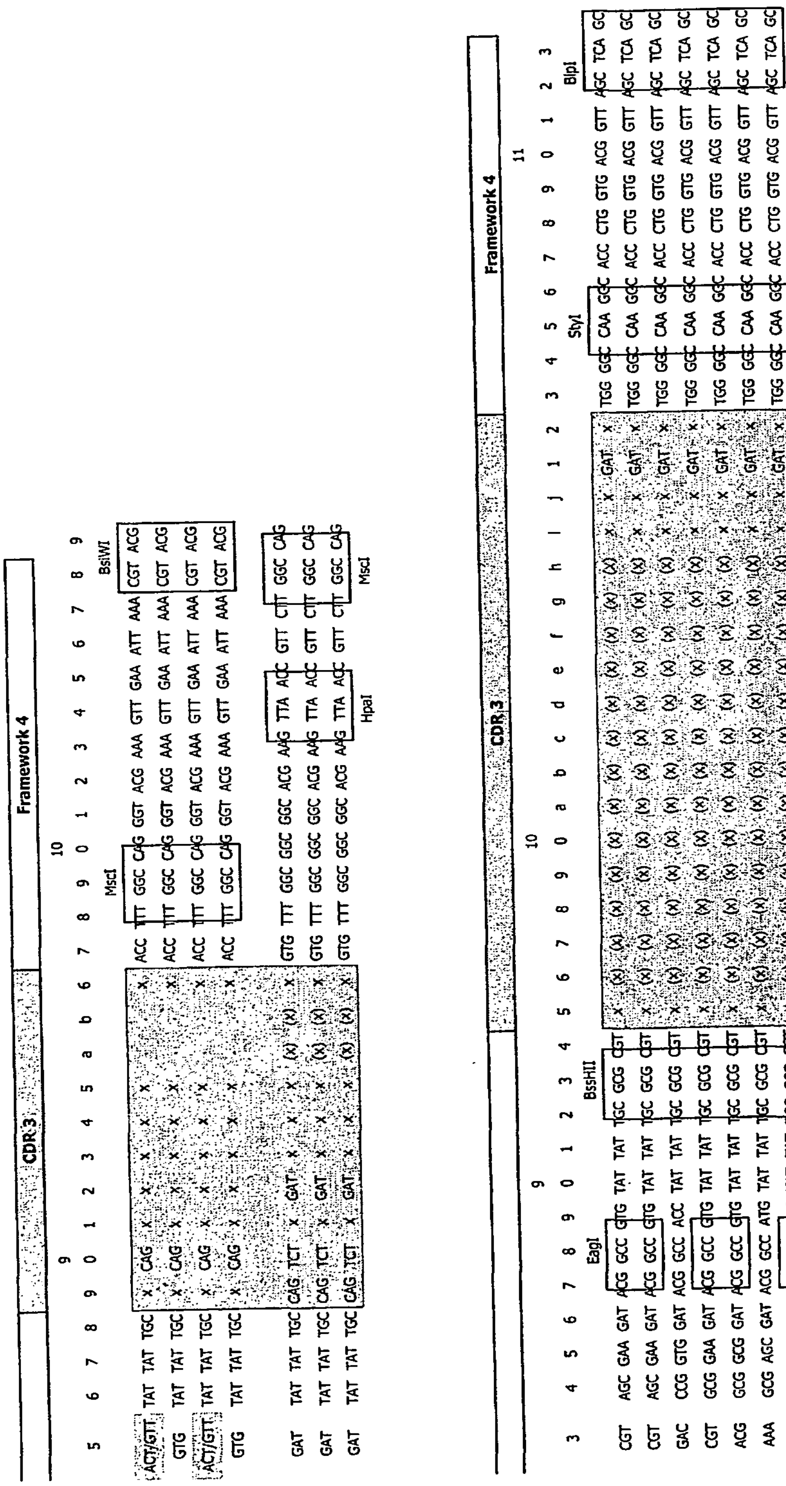
CDR 3
Framework 4
9
10
5 6 7 8 9 0 1 2 3 4 5 a b 6 7 8 9 0 1 2 3 4 5 6 7 8 9
MscI
BsiWI
ACT/GTT TAT TAT TGC x CAG x x x x x x ACC TTT GGC CAG GGT ACG AAA GTT GAA ATT AAA CGT ACG
GTG TAT TAT TGC x CAG x x x x x x ACC TTT GGC CAG GGT ACG AAA GTT GAA ATT AAA CGT ACG
ACT/GTT TAT TAT TGC x CAG x x x x x x ACC TTT GGC CAG GGT ACG AAA GTT GAA ATT AAA CGT ACG
GTG TAT TAT TGC x CAG x x x x x x ACC TTT GGC CAG GGT ACG AAA GTT GAA ATT AAA CGT ACG
GAT TAT TAT TGC CAG TCT x GAT x x x (x) (x) x GTG TTT GGC GGC GGC ACG AAG TTA ACC GTT CTT GGC CAG
GAT TAT TAT TGC CAG TCT x GAT x x x (x) (x) x GTG TTT GGC GGC GGC ACG AAG TTA ACC GTT CTT GGC CAG
GAT TAT TAT TGC CAG TCT x GAT x x x (x) (x) x GTG TTT GGC GGC GGC ACG AAG TTA ACC GTT CTT GGC CAG
HpaI
MscI
CDR 3
Framework 4
9
10
11
3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 a b c d e f g h i j 1 2 3 4 5 6 7 8 9 0 1 2 3
EagI
BssHII
StyI
BlpI
CGT AGC GAA GAT ACG GCC GTG TAT TAT TGC GCG CGT x (x) (x) (x) (x) (x) (x) (x) (x) (x) (x) (x) (x) (x) x x GAT x TGG GGC CAA GGC ACC CTG GTG ACG GTT AGC TCA GC
CGT AGC GAA GAT ACG GCC GTG TAT TAT TGC GCG CGT x (x) (x) (x) (x) (x) (x) (x) (x) (x) (x) (x) (x) (x) x x GAT x TGG GGC CAA GGC ACC CTG GTG ACG GTT AGC TCA GC
GAC CCG GTG GAT ACG GCC ACC TAT TAT TGC GCG CGT x (x) (x) (x) (x) (x) (x) (x) (x) (x) (x) (x) (x) (x) x x GAT x TGG GGC CAA GGC ACC CTG GTG ACG GTT AGC TCA GC
CGT GCG GAA GAT ACG GCC GTG TAT TAT TGC GCG CGT x (x) (x) (x) (x) (x) (x) (x) (x) (x) (x) (x) (x) (x) x x GAT x TGG GGC CAA GGC ACC CTG GTG ACG GTT AGC TCA GC
ACG GCG GCG GAT ACG GCC GTG TAT TAT TGC GCG CGT x (x) (x) (x) (x) (x) (x) (x) (x) (x) (x) (x) (x) (x) x x GAT x TGG GGC CAA GGC ACC CTG GTG ACG GTT AGC TCA GC
AAA GCG AGC GAT ACG GCC ATG TAT TAT TGC GCG CGT x (x) (x) (x) (x) (x) (x) (x) (x) (x) (x) (x) (x) (x) x x GAT x TGG GGC CAA GGC ACC CTG GTG ACG GTT AGC TCA GC
ACC CCG GAA GAT ACG GCC GTG TAT TAT TGC GCG CGT x (x) (x) (x) (x) (x) (x) (x) (x) (x) (x) (x) (x) (x) x x GAT x TGG GGC CAA GGC ACC CTG GTG ACG GTT AGC TCA GC

FIG. 2, cont.

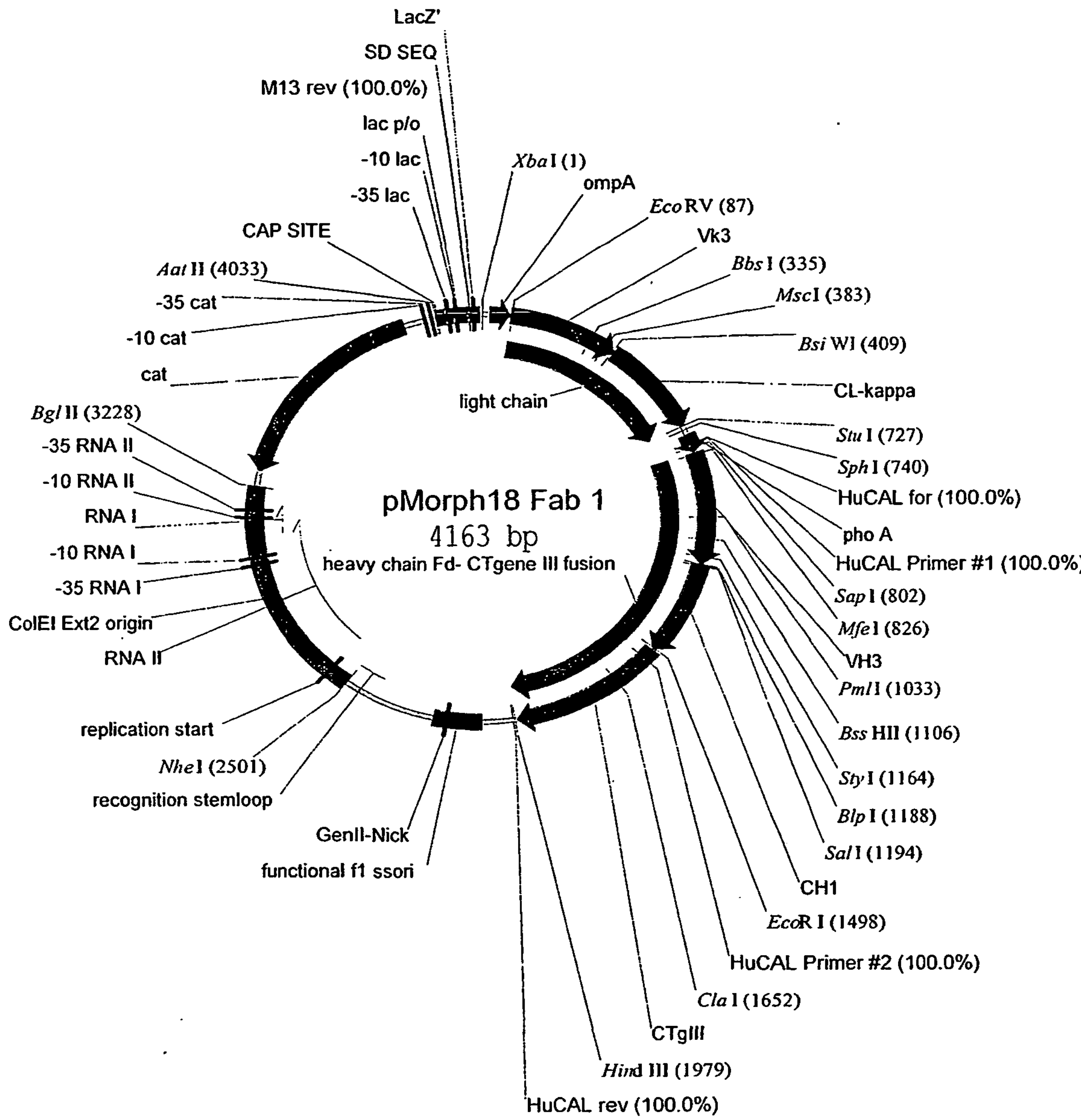
pMorph18 Fab 1
4163 bp
heavy chain Fd- CTgene III fusion
light chain
LacZ'
SD SEQ
M13 rev (100.0%)
lac p/o
-10 lac
-35 lac
CAP SITE
AatII (4033)
-35 cat
-10 cat
cat
BglII (3228)
-35 RNA II
-10 RNA II
RNA I
-10 RNA I
-35 RNA I
ColEI Ext2 origin
RNA II
replication start
NheI (2501)
recognition stemloop
GenII-Nick
functional f1 ssori
XbaI (1)
ompA
EcoRV (87)
Vk3
BbsI (335)
MscI (383)
BsiWI (409)
CL-kappa
StuI (727)
SphI (740)
HuCAL for (100.0%)
pho A
HuCAL Primer #1 (100.0%)
SapI (802)
MfeI (826)
VH3
PmlI (1033)
BssHII (1106)
StyI (1164)
BlpI (1188)
SalI (1194)
CH1
EcoRI (1498)
HuCAL Primer #2 (100.0%)
ClaI (1652)
CTgIII
HindIII (1979)
HuCAL rev (100.0%)

FIG. 3

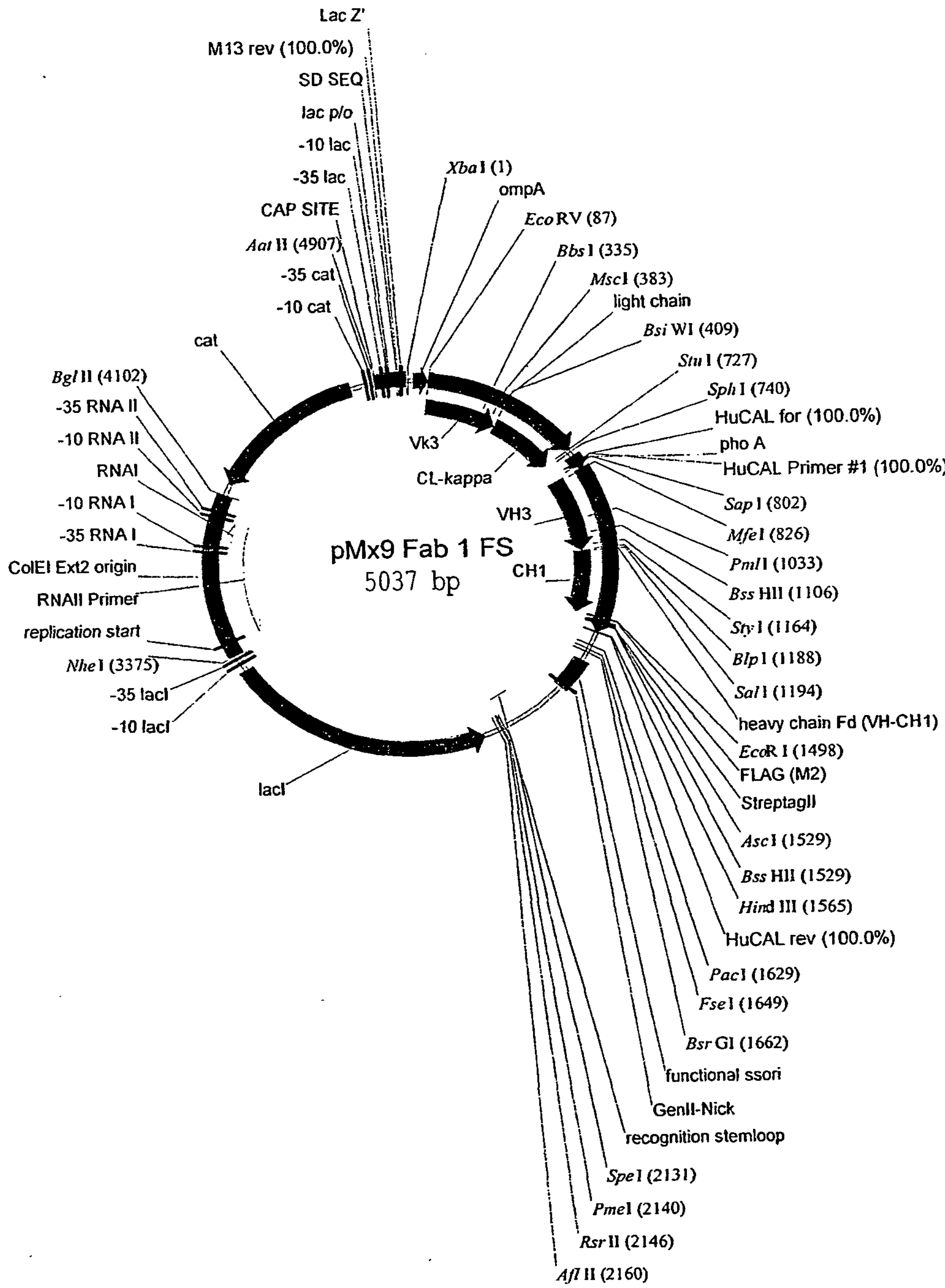
pMx9 Fab 1 FS
5037 bp
Lac Z'
M13 rev (100.0%)
SD SEQ
lac p/o
-10 lac
-35 lac
CAP SITE
AatII (4907)
-35 cat
-10 cat
cat
BglII (4102)
-35 RNA II
-10 RNA II
RNAI
-10 RNA I
-35 RNA I
ColEI Ext2 origin
RNAII Primer
replication start
NheI (3375)
-35 lacI
-10 lacI
lacI
XbaI (1)
ompA
EcoRV (87)
BbsI (335)
MscI (383)
light chain
BsiWI (409)
StuI (727)
SphI (740)
HuCAL for (100.0%)
pho A
HuCAL Primer #1 (100.0%)
SapI (802)
MfeI (826)
PmlI (1033)
BssHII (1106)
StyI (1164)
BlpI (1188)
SalI (1194)
heavy chain Fd (VH-CH1)
EcoRI (1498)
FLAG (M2)
StreptagII
AscI (1529)
BssHII (1529)
HindIII (1565)
HuCAL rev (100.0%)
PacI (1629)
FseI (1649)
BsrGI (1662)
functional ssori
GenII-Nick
recognition stemloop
SpeI (2131)
PmeI (2140)
RsrII (2146)
AflII (2160)
Vk3
CL-kappa
VH3
CH1

FIG. 4

FIG. 5

```
TIMP1_human 135850     1 CTCVPPHPQTAFCNSDLVIRAKFVGTPEVNQTTLYQRYEIKMTKMYKGFQ  50
TIMP1_rat 1174697      1 CSCAPTHPQTAFCNSDLVIRAKFMGSPEIIETTLYQRYEIKMTKMLKGFD  50
                         *.* * *****************.*.**. .************** ***

TIMP1_human 135850    51 ALGDAADIRFVYTPAMESVCGYFHRSHNRSEEFLIAGKLQDGLLHITTCS 100
TIMP1_rat 1174697     51 AVGNATGFRFAYTPAMESLCGYVHKSQNRSEEFLIAGRLRNGNLHITACS 100
                         *.* *.  ** *******.*** *.*.**********.*. * ****.**

TIMP1_human 135850   101 FVAPWNSLSLAQRRGFTKTYTVGCEECTVFPCLSIPCKLQSGTHCLWTDQ 150
TIMP1_rat 1174697    101 FLVPWHNLSPAQQKAFVKTYSAGCGVCTVFPCSAIPCKLESDSHCLWTDQ 150
                         *. **. ** **.. * ***. **  ****** .*****.* .*******

TIMP1_human 135850   151 LLQGSEKGFQSRHLACLPREPGLCTWQSLRSQIA           184
TIMP1_rat 1174697    151 ILMGSEKGYQSDHFACLPRNPDLCTWQYLGVSMTRSLPLAKAEA 194
                         .* *****.** * ***** * ***** *   ..
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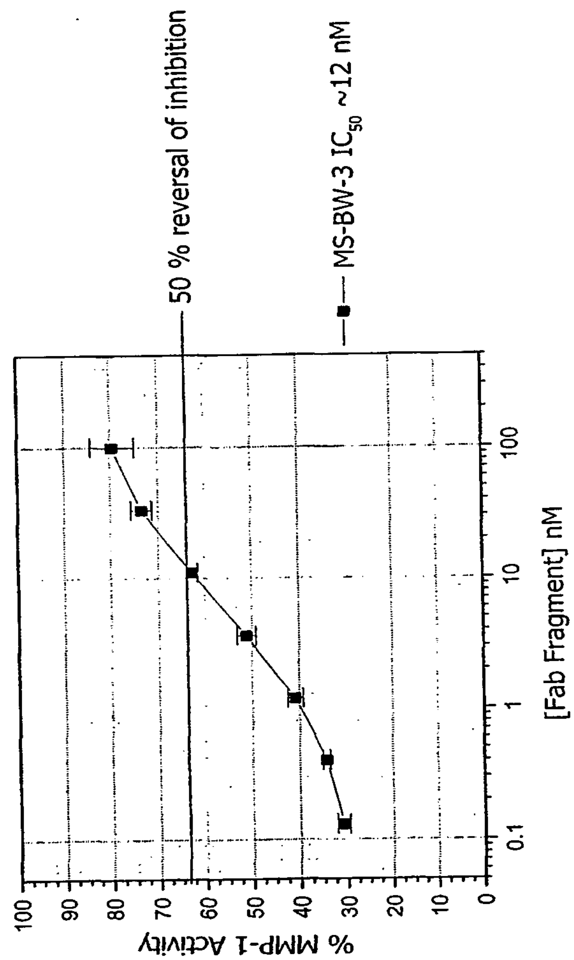

50 % reversal of inhibition
MS-BW-3 IC$_{50}$ ~12 nM
% MMP-1 Activity
100
90
80
70
60
50
40
30
20
10
0
0.1
1
10
100
[Fab Fragment] nM

FIG. 6

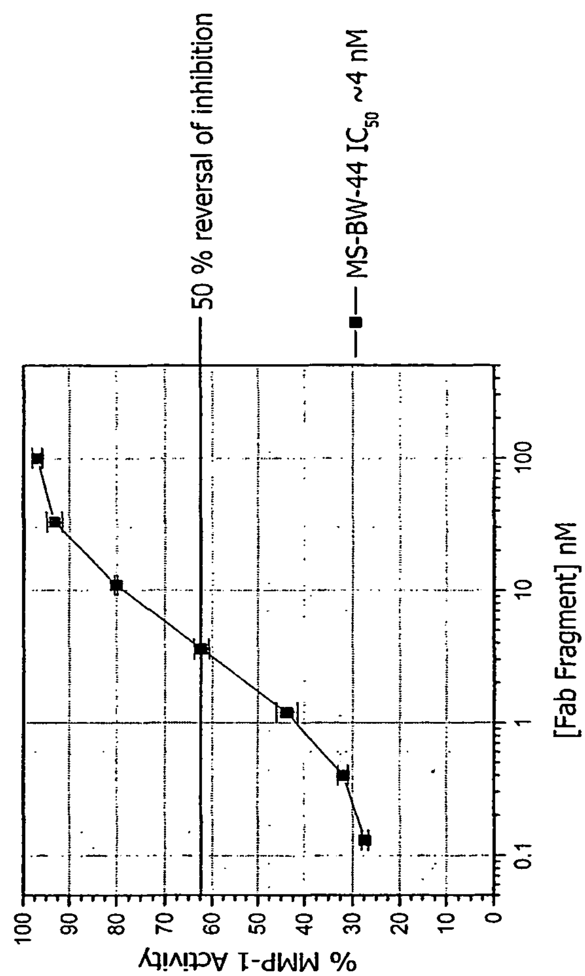

50 % reversal of inhibition
MS-BW-44 IC50 ~4 nM
% MMP-1 Activity
100
90
80
70
60
50
40
30
20
10
0
0.1
1
10
100
[Fab Fragment] nM

FIG. 7

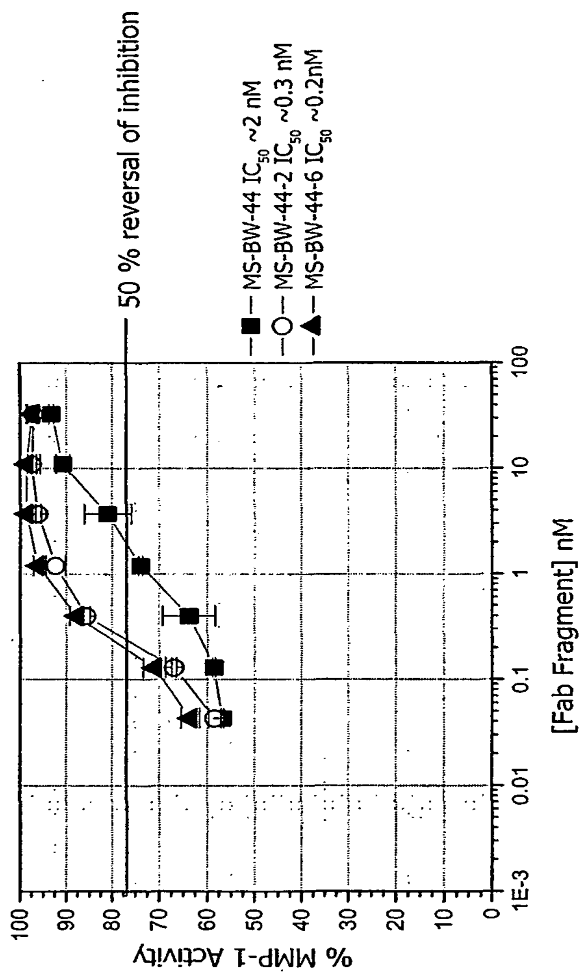

50 % reversal of inhibition
MS-BW-44 IC50 ~2 nM
MS-BW-44-2 IC50 ~0.3 nM
MS-BW-44-6 IC50 ~0.2nM
% MMP-1 Activity
[Fab Fragment] nM
1E-3
0.01
0.1
1
10
100
0
10
20
30
40
50
60
70
80
90
100

FIG. 8

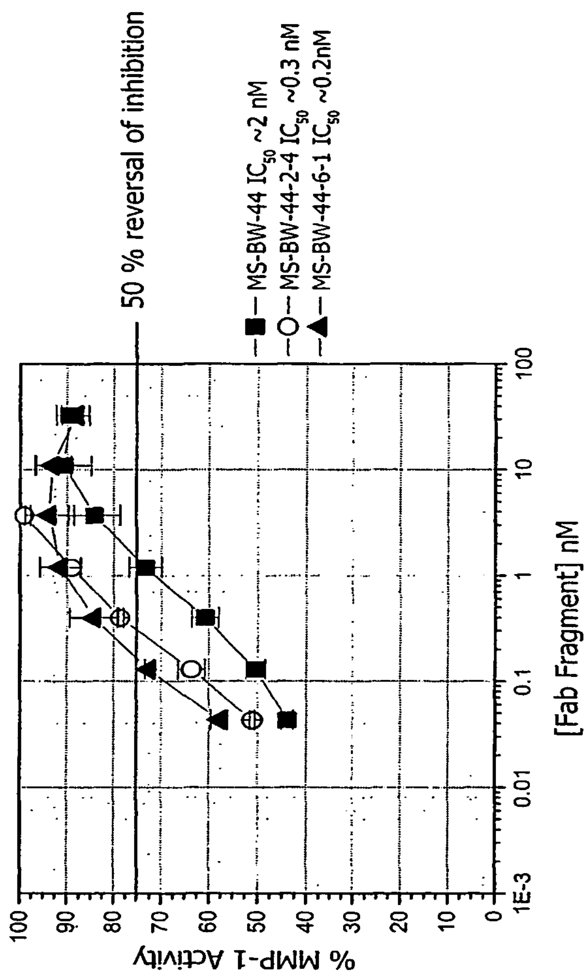

50 % reversal of inhibition
—■— MS-BW-44 IC50 ~2 nM
—○— MS-BW-44-2-4 IC50 ~0.3 nM
—▲— MS-BW-44-6-1 IC50 ~0.2nM
% MMP-1 Activity
100
90
80
70
60
50
40
30
20
10
0
1E-3
0.01
0.1
1
10
100
[Fab Fragment] nM

FIG. 9

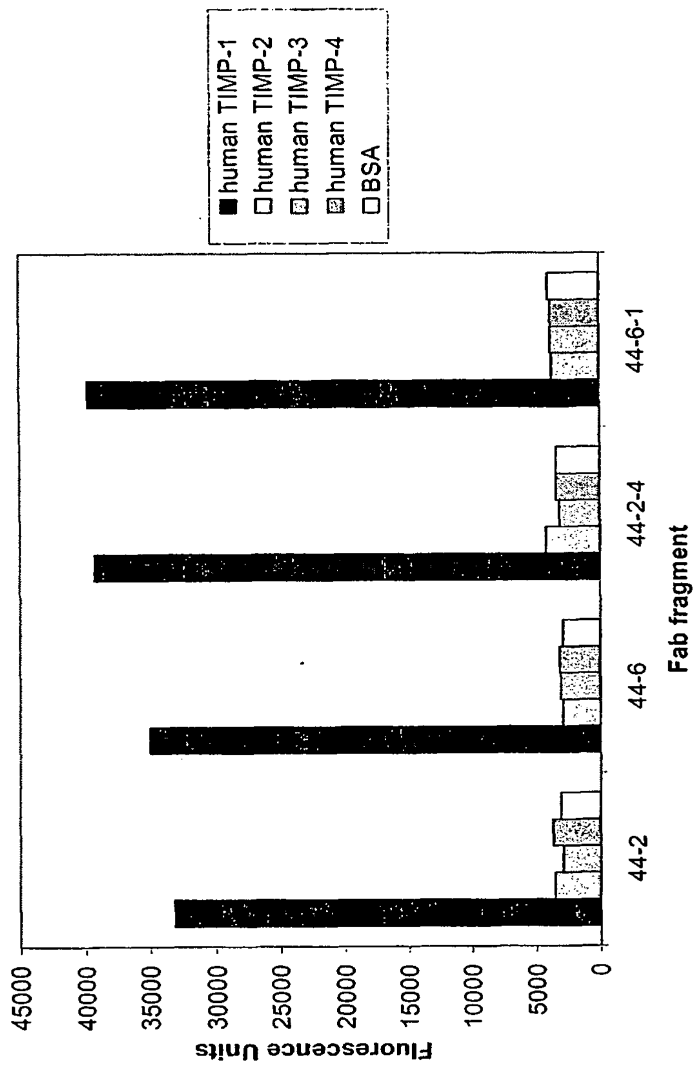

human TIMP-1
human TIMP-2
human TIMP-3
human TIMP-4
BSA
Fluorescence Units
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
44-2
44-6
44-2-4
44-6-1
Fab fragment

FIG. 10

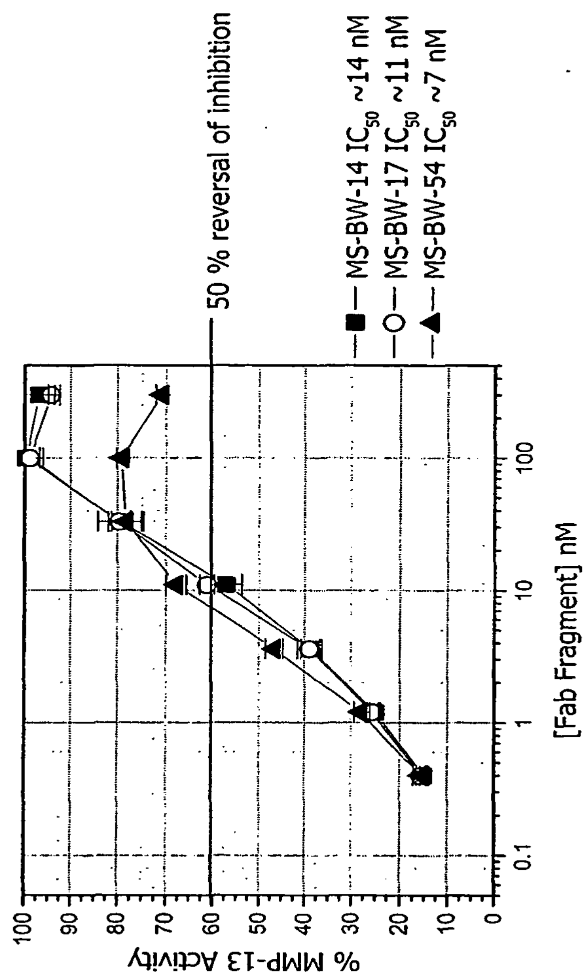

50 % reversal of inhibition
—■— MS-BW-14 IC50 ~14 nM
—O— MS-BW-17 IC50 ~11 nM
—▲— MS-BW-54 IC50 ~7 nM
% MMP-13 Activity
0
10
20
30
40
50
60
70
80
90
100
0.1
1
10
100
[Fab Fragment] nM

FIG. 11

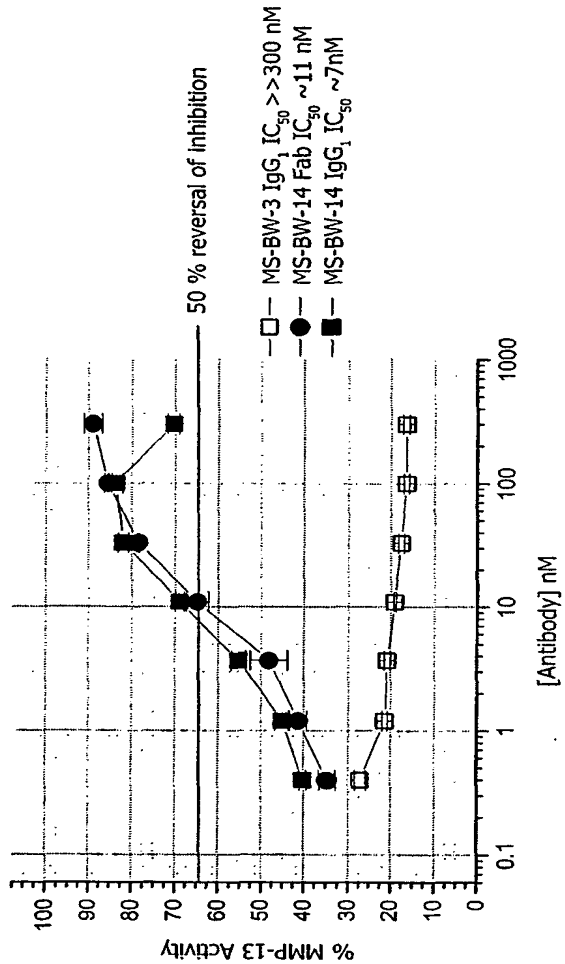

50 % reversal of inhibition
MS-BW-3 IgG1 IC50 >>300 nM
MS-BW-14 Fab IC50 ~11 nM
MS-BW-14 IgG1 IC50 ~7nM
% MMP-13 Activity
100
90
80
70
60
50
40
30
20
10
0
0.1
1
10
100
1000
[Antibody] nM

FIG. 12

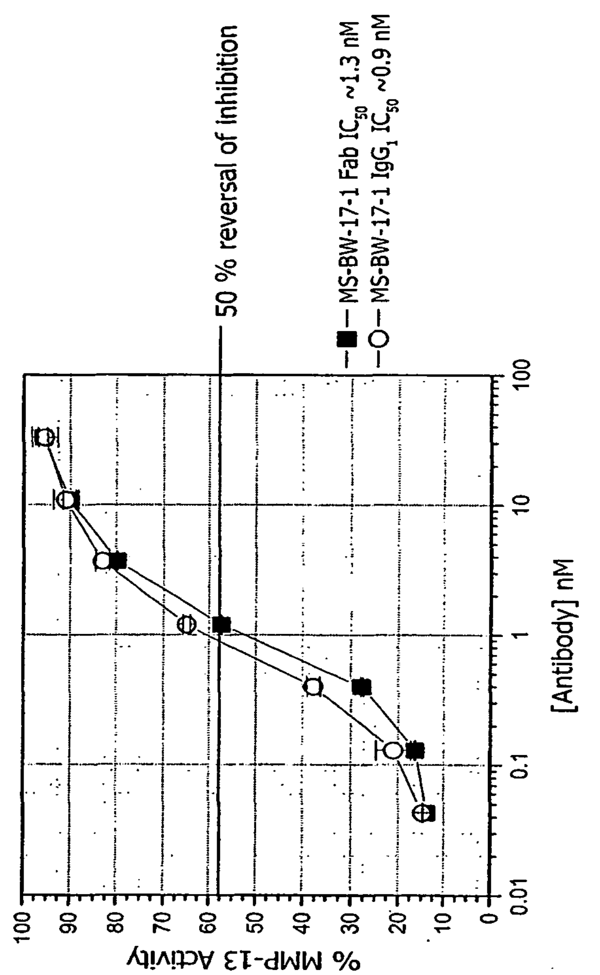

% MMP-13 Activity
100
90
80
70
60
50
40
30
20
10
0
0.01
0.1
1
10
100
[Antibody] nM
50 % reversal of inhibition
MS-BW-17-1 Fab IC_{50} ~1.3 nM
MS-BW-17-1 IgG_1 IC_{50} ~0.9 nM

FIG. 13

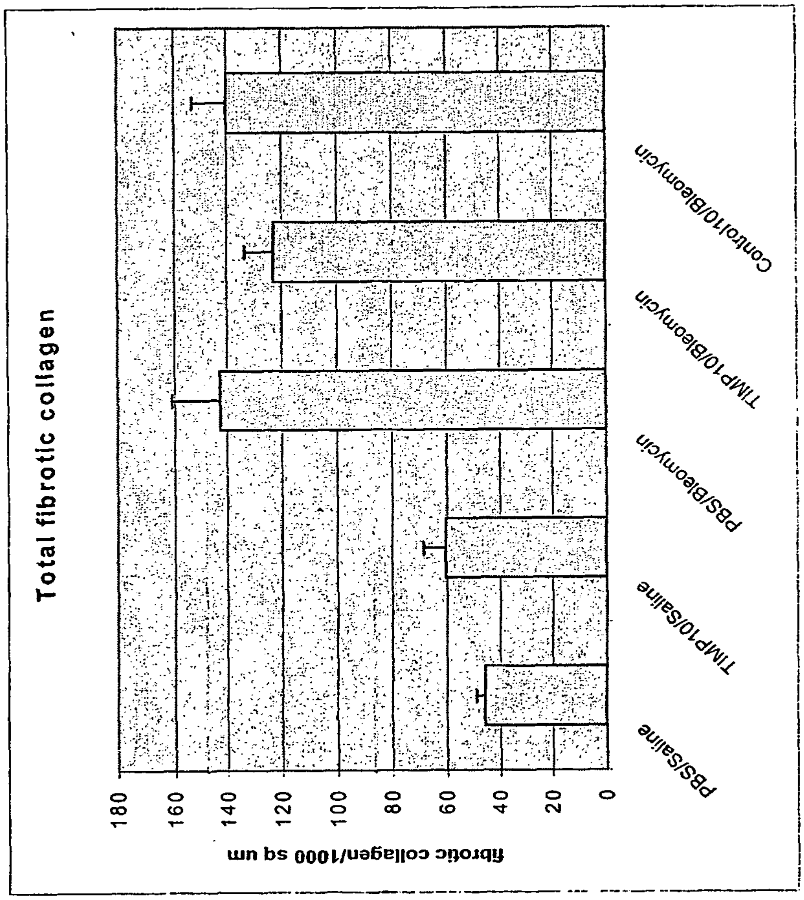
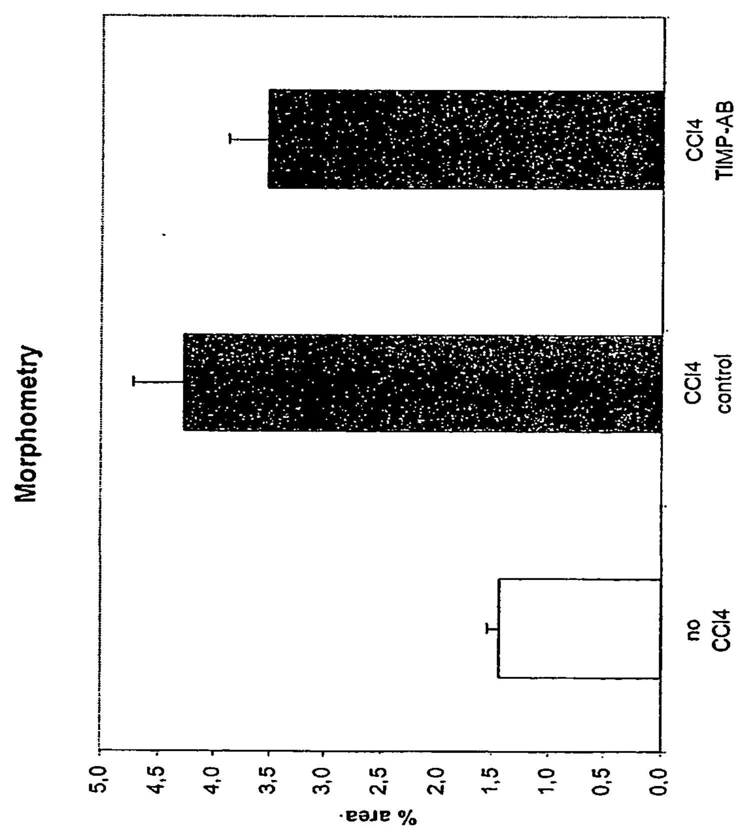

Total fibrotic collagen
fibrotic collagen/1000 sq um
0
20
40
60
80
100
120
140
160
180
PBS/Saline
TIMP10/Saline
PBS/Bleomycin
TIMP10/Bleomycin
Control10/Bleomycin

FIG. 14

FIG. 15


Morphometry
% area
5,0
4,5
4,0
3,5
3,0
2,5
2,0
1,5
1,0
0,5
0,0
no CCl4
CCl4 control
CCl4 TIMP-AB

SEQUENCE LISTING

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MorphoSys AG

<120> Human TIMP-1 Antibodies

<130> 02973.00074

<150> US 60/285,683
<151> 2001-04-24

<160> 381

<170> FastSEQ for Windows Version 4.0

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Gly Phe Asp Tyr
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Phe Leu Asp Ile
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 1               5                   10

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 1               5                   10

<210> 10
```

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1 5

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1 5 10 15
Val

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1 5

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Gly Tyr Ala Asp Ile Ser Phe Asp Tyr
1 5

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```
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Leu Ile Gly Tyr Phe Asp Leu
 1               5

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 1               5                   10

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 1               5                   10

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 1               5                   10
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Ser Gly Tyr Leu Asp Tyr
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Asp Tyr

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Phe Arg Ala Tyr Gly Asp Asp Phe Tyr Phe Asp Val
 1   5   10

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<223> Xaa = Any Amino Acid

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 1   5   10   15

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Tyr Tyr Val Thr Asp Thr Ala Tyr Phe Asp Tyr

1 5 10

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1 5 10

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1 5

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1 5

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Leu Phe Ala Gly Leu Glu Leu Tyr Phe Asp Tyr
1 5 10

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Gly Tyr Ile Pro Tyr His Leu Phe Asp Tyr
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1 5

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1 5 10

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1 5 10 15

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Ile Ile Gly Asp Tyr Val Ile Phe Phe Asp Val
1 5 10

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Leu Phe Thr Tyr Pro Phe Leu Tyr Phe Asp Val
1 5 10

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1 5 10

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Gln Ser Trp Asp Ile His Pro Phe Asp Val
1 5 10

<210> 59

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<400> 59
Gln Ser Trp Asp Leu Glu Pro Tyr
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<400> 60
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1 5

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<400> 61
Gln Ser Tyr Asp Pro Ser His Pro Ser Lys
1 5 10

<210> 62
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<212> PRT
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<400> 62
Gln Ser Tyr Asp Asp Met Gln Phe
1 5

<210> 63
<211> 9
<212> PRT
<213> Homo sapiens

<400> 63
Gln Ser Trp Asp Ile Asn His Ala Ile
1 5

<210> 64
<211> 9
<212> PRT
<213> Homo sapiens

<400> 64

Gln Ser Tyr Asp Tyr Tyr Asp Tyr Gly
1 5

<210> 65
<211> 8
<212> PRT
<213> Homo sapiens

<400> 65
Gln Gln Ala Asn Asp Phe Pro Ile
1 5

<210> 66
<211> 10
<212> PRT
<213> Homo sapiens

<400> 66
Gln Ser Trp Asp Asn Leu Lys Met Pro Val
1 5 10

<210> 67
<211> 10
<212> PRT
<213> Homo sapiens

<400> 67
Gln Ser Tyr Asp Val Phe Pro Ile Asn Arg
1 5 10

<210> 68
<211> 7
<212> PRT
<213> Homo sapiens

<400> 68
Gln Ser Asp Leu Tyr Phe Pro
1 5

<210> 69
<211> 8
<212> PRT
<213> Homo sapiens

<400> 69
Gln Ser Tyr Asp Val Thr Pro Arg
1 5

<210> 70
<211> 9

<212> PRT
<213> Homo sapiens

<400> 70
Gln Ser Tyr Asp Pro Val Gly Phe Pro
1 5

<210> 71
<211> 8
<212> PRT
<213> Homo sapiens

<400> 71
Gln Ser Tyr Asp Leu Ser Pro Arg
1 5

<210> 72
<211> 10
<212> PRT
<213> Homo sapiens

<400> 72
Gln Ser Tyr Asp Phe Ser His Tyr Phe Phe
1 5 10

<210> 73
<211> 9
<212> PRT
<213> Homo sapiens

<400> 73
Gln Ser Tyr Asp Leu Arg Tyr Ser His
1 5

<210> 74
<211> 8
<212> PRT
<213> Homo sapiens

<400> 74
Gln Ser Tyr Asp Leu Arg Asn Arg
1 5

<210> 75
<211> 9
<212> PRT
<213> Homo sapiens

<400> 75
Gln Ser Tyr Asp Phe Thr Tyr Gly Ser

1 5

<210> 76
<211> 8
<212> PRT
<213> Homo sapiens

<400> 76
Gln Gln Phe Asn Asp Ser Pro Tyr
1 5

<210> 77
<211> 9
<212> PRT
<213> Homo sapiens

<400> 77
Gln Ser Tyr Asp Ile Ser Gly Tyr Pro
1 5

<210> 78
<211> 10
<212> PRT
<213> Homo sapiens

<400> 78
Gln Ser Arg Asp Leu Tyr Tyr Val Tyr Tyr
1 5 10

<210> 79
<211> 8
<212> PRT
<213> Homo sapiens

<400> 79
Gln Ser Tyr Asp Arg Ser Met Trp
1 5

<210> 80
<211> 9
<212> PRT
<213> Homo sapiens

<400> 80
Gln Ser Trp Asp Val Gln Thr Asp Lys
1 5

<210> 81
<211> 9
<212> PRT

<213> Homo sapiens

<400> 81
Gln Ser Trp Asp Pro Ser His Tyr Tyr
1 5

<210> 82
<211> 9
<212> PRT
<213> Homo sapiens

<400> 82
Gln Ser Tyr Asp Ile Met Pro Glu Arg
1 5

<210> 83
<211> 9
<212> PRT
<213> Homo sapiens

<400> 83
Gln Ser Met Asp Phe Arg Leu Met His
1 5

<210> 84
<211> 9
<212> PRT
<213> Homo sapiens

<400> 84
Gln Ser Phe Asp Met Ile His Pro Tyr
1 5

<210> 85
<211> 7
<212> PRT
<213> Homo sapiens

<400> 85
Gln Ser Asp Phe Pro Val Met
1 5

<210> 86
<211> 7
<212> PRT
<213> Homo sapiens

<400> 86
Gln Ser Asp Asn Pro Tyr Leu
1 5

<210> 87
<211> 11
<212> PRT
<213> Homo sapiens

<400> 87
Thr Cys Val Pro Pro His Pro Gln Thr Ala Phe
1 5 10

<210> 88
<211> 12
<212> PRT
<213> Homo sapiens

<400> 88
Cys Thr Ser Val Pro Pro His Pro Gln Thr Ala Phe
1 5 10

<210> 89
<211> 12
<212> PRT
<213> Homo sapiens

<400> 89
Ser Thr Cys Val Pro Pro His Pro Gln Thr Ala Phe
1 5 10

<210> 90
<211> 13
<212> PRT
<213> Homo sapiens

<400> 90
Ser Thr Ser Val Pro Pro His Pro Gln Thr Ala Phe Cys
1 5 10

<210> 91
<211> 10
<212> PRT
<213> Homo sapiens

<400> 91
Cys Glu Val Asn Gln Thr Thr Leu Tyr Gln
1 5 10

<210> 92
<211> 12
<212> PRT
<213> Homo sapiens

<400> 92
Pro Ala Met Glu Ser Val Cys Gly Tyr Phe His Arg
1 5 10

<210> 93
<211> 16
<212> PRT
<213> Homo sapiens

<400> 93
Pro Ala Met Glu Ser Val Cys Gly Tyr Phe His Arg Ser His Asn Arg
1 5 10 15

<210> 94
<211> 17
<212> PRT
<213> Homo sapiens

<400> 94
Cys Pro Ala Met Glu Ser Val Ser Gly Tyr Phe His Arg Ser His Asn
1 5 10 15
Arg

<210> 95
<211> 17
<212> PRT
<213> Homo sapiens

<400> 95
Pro Ala Met Glu Ser Val Ser Gly Tyr Phe His Arg Ser His Asn Arg
1 5 10 15
Cys

<210> 96
<211> 12
<212> PRT
<213> Homo sapiens

<400> 96
Cys Leu Trp Thr Asp Gln Leu Leu Gln Gly Ser Glu
1 5 10

<210> 97
<211> 215
<212> PRT
<213> Homo sapiens

<400> 97
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1   5   10   15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20   25   30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35   40   45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50   55   60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65   70   75   80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Tyr Gln
                85   90   95
Gln Phe Thr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100   105   110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115   120   125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130   135   140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145   150   155   160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165   170   175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180   185   190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195   200   205
Thr Val Ala Pro Thr Glu Ala
    210   215

<210> 98
<211> 215
<212> PRT
<213> Homo sapiens

<400> 98
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1   5   10   15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20   25   30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35   40   45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50   55   60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65   70   75   80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Lys
                85   90   95
Thr Tyr Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100   105   110

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Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145                 150                 155                 160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205
Thr Val Ala Pro Thr Glu Ala
    210                 215

<210> 99
<211> 211
<212> PRT
<213> Homo sapiens

<400> 99
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Leu
                85                  90                  95
Arg Phe Ser Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145                 150                 155                 160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205
Thr Val Ala
    210
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<210> 100
<211> 215
<212> PRT
<213> Homo sapiens

<400> 100
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Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Ile
                85                  90                  95
Asn Val Ile Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145                 150                 155                 160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205
Thr Val Ala Pro Thr Glu Ala
    210                 215
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<210> 101
<211> 215
<212> PRT
<213> Homo sapiens

<400> 101
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Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
```

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65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Val
                85                  90                  95
Arg Phe Met Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145                 150                 155                 160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205
Thr Val Ala Pro Thr Glu Ala
    210                 215

<210> 102
<211> 215
<212> PRT
<213> Homo sapiens

<400> 102
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1              5                   10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Tyr
                85                  90                  95
Lys Phe Asn Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145                 150                 155                 160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190
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Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205
Thr Val Ala Pro Thr Glu Ala
    210                 215

<210> 103
<211> 215
<212> PRT
<213> Homo sapiens

<400> 103
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Arg
                85                  90                  95
Arg Phe Ser Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145                 150                 155                 160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205
Thr Val Ala Pro Thr Glu Ala
    210                 215

<210> 104
<211> 214
<212> PRT
<213> Homo sapiens

<400> 104
Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
 1               5                  10                  15
Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
            20                  25                  30
```

```
Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45
Ile Tyr Asp Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60
Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65                  70                  75                  80
Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Arg Asp Phe Asn Arg
                85                  90                  95
Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
            100                 105                 110
Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
        115                 120                 125
Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
    130                 135                 140
Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
145                 150                 155                 160
Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
                165                 170                 175
Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
            180                 185                 190
Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
        195                 200                 205
Val Ala Pro Thr Glu Ala
    210

<210> 105
<211> 213
<212> PRT
<213> Homo sapiens

<400> 105
Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
 1               5                  10                  15
Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
            20                  25                  30
Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45
Ile Tyr Asp Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60
Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65                  70                  75                  80
Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Gln Arg Lys
                85                  90                  95
Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
            100                 105                 110
Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
        115                 120                 125
Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
    130                 135                 140
Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
```

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145                 150                 155                 160
Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
                165                 170                 175
Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
            180                 185                 190
Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
        195                 200                 205
Ala Pro Thr Glu Ala
    210
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<210> 106
<211> 215
<212> PRT
<213> Homo sapiens

<400> 106

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Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1               5                  10                  15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
            20                  25                  30
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35                  40                  45
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
    50                  55                  60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65                  70                  75                  80
Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Tyr Gly Thr Ser
                85                  90                  95
Val Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
            100                 105                 110
Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
        115                 120                 125
Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
    130                 135                 140
Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145                 150                 155                 160
Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
                165                 170                 175
Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
            180                 185                 190
Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
        195                 200                 205
Ser Phe Asn Arg Gly Glu Ala
    210                 215
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<210> 107
<211> 214
<212> PRT
<213> Homo sapiens

<400> 107
Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15
Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30
Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45
Ile Tyr Asp Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60
Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65 70 75 80
Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Gly Phe Lys
85 90 95
Thr His Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
100 105 110
Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
115 120 125
Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
130 135 140
Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
145 150 155 160
Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
165 170 175
Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
180 185 190
Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
195 200 205
Val Ala Pro Thr Glu Ala
210

<210> 108
<211> 211
<212> PRT
<213> Homo sapiens

<400> 108
Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15
Thr Ala Arg Ile Ser Cys Ser Gly Asp Ala Leu Gly Asp Lys Tyr Ala
20 25 30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45
Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Tyr Ser Leu Leu Val
85 90 95
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
100 105 110

Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
115 120 125
Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
130 135 140
Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
145 150 155 160
Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
165 170 175
Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
180 185 190
Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
195 200 205
Thr Glu Ala
210

<210> 109
<211> 211
<212> PRT
<213> Homo sapiens

<400> 109
Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15
Thr Ala Arg Ile Ser Cys Ser Gly Asp Ala Leu Gly Asp Lys Tyr Ala
20 25 30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45
Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Asn Phe His Val
85 90 95
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
100 105 110
Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
115 120 125
Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
130 135 140
Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
145 150 155 160
Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
165 170 175
Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
180 185 190
Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
195 200 205
Thr Glu Ala
210

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<210> 110
<211> 216
<212> PRT
<213> Homo sapiens

<400> 110
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1              5                   10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Met Ile
                85                  90                  95
Ala Arg Tyr Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110
Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
        115                 120                 125
Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
    130                 135                 140
Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
145                 150                 155                 160
Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
                165                 170                 175
Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
            180                 185                 190
His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
        195                 200                 205
Lys Thr Val Ala Pro Thr Glu Ala
    210                 215

<210> 111
<211> 213
<212> PRT
<213> Homo sapiens

<400> 111
Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
 1              5                   10                  15
Thr Ala Arg Ile Ser Cys Ser Gly Asp Ala Leu Gly Asp Lys Tyr Ala
            20                  25                  30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        35                  40                  45
Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50                  55                  60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
```

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65                      70                      75                      80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp Ile His Pro Phe Asp
                    85                      90                      95
Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
            100                     105                     110
Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
        115                     120                     125
Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
    130                     135                     140
Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145                     150                     155                     160
Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
                    165                     170                     175
Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
            180                     185                     190
Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
        195                     200                     205
Ala Pro Thr Glu Ala
    210

<210> 112
<211> 213
<212> PRT
<213> Homo sapiens

<400> 112
Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
 1               5                  10                  15
Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
            20                  25                  30
Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45
Ile Tyr Asp Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60
Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65                  70                  75                  80
Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp Leu Glu Pro
                85                  90                  95
Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
            100                 105                 110
Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
        115                 120                 125
Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
    130                 135                 140
Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145                 150                 155                 160
Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
                165                 170                 175
Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
            180                 185                 190
```

```
Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
        195                 200                 205
Ala Pro Thr Glu Ala
    210

<210> 113
<211> 215
<212> PRT
<213> Homo sapiens

<400> 113
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Val Leu
                85                  90                  95
Asp Ser Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145                 150                 155                 160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205
Thr Val Ala Pro Thr Glu Ala
    210                 215

<210> 114
<211> 216
<212> PRT
<213> Homo sapiens

<400> 114
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
```

```
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Pro Ser
                85                  90                  95
His Pro Ser Lys Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110
Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
        115                 120                 125
Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
    130                 135                 140
Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
145                 150                 155                 160
Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
                165                 170                 175
Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
            180                 185                 190
His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
        195                 200                 205
Lys Thr Val Ala Pro Thr Glu Ala
    210                 215

<210> 115
<211> 214
<212> PRT
<213> Homo sapiens

<400> 115
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Asp Met
                85                  90                  95
Gln Phe Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
            100                 105                 110
Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
        115                 120                 125
Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
    130                 135                 140
Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
```

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145                 150                 155                 160
Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
                165                 170                 175
Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
            180                 185                 190
Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
        195                 200                 205
Val Ala Pro Thr Glu Ala
    210
```

<210> 116
<211> 215
<212> PRT
<213> Homo sapiens

<400> 116

```
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                   10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp Ile Asn
                85                  90                  95
His Ala Ile Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145                 150                 155                 160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205
Thr Val Ala Pro Thr Glu Ala
    210                 215
```

<210> 117
<211> 215
<212> PRT
<213> Homo sapiens

<400> 117
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Tyr Tyr
85 90 95
Asp Tyr Gly Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
115 120 125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
130 135 140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145 150 155 160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
165 170 175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
180 185 190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
195 200 205
Thr Val Ala Pro Thr Glu Ala
210 215

<210> 118
<211> 215
<212> PRT
<213> Homo sapiens

<400> 118
Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
50 55 60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65 70 75 80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ala Asn Asp Phe Pro
85 90 95
Ile Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
100 105 110

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
115 120 125
Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
130 135 140
Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145 150 155 160
Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
165 170 175
Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
180 185 190
Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
195 200 205
Ser Phe Asn Arg Gly Glu Ala
210 215

<210> 119
<211> 216
<212> PRT
<213> Homo sapiens

<400> 119
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp Asn Leu
85 90 95
Lys Met Pro Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110
Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
115 120 125
Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
130 135 140
Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
145 150 155 160
Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
165 170 175
Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
180 185 190
His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
195 200 205
Lys Thr Val Ala Pro Thr Glu Ala
210 215

<210> 120
<211> 216
<212> PRT
<213> Homo sapiens

<400> 120
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1   5   10   15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20   25   30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35   40   45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50   55   60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65   70   75   80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Val Phe
                85   90   95
Pro Ile Asn Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100   105   110
Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
        115   120   125
Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
    130   135   140
Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
145   150   155   160
Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
                165   170   175
Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
            180   185   190
His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
        195   200   205
Lys Thr Val Ala Pro Thr Glu Ala
    210   215

<210> 121
<211> 213
<212> PRT
<213> Homo sapiens

<400> 121
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1   5   10   15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20   25   30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35   40   45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50   55   60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu

```
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Asp Leu Tyr Phe
                85                  90                  95
Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
            100                 105                 110
Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
        115                 120                 125
Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
    130                 135                 140
Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145                 150                 155                 160
Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
                165                 170                 175
Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
            180                 185                 190
Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
        195                 200                 205
Ala Pro Thr Glu Ala
    210

<210> 122
<211> 214
<212> PRT
<213> Homo sapiens

<400> 122
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Val Thr
                85                  90                  95
Pro Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
            100                 105                 110
Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
        115                 120                 125
Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
    130                 135                 140
Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
145                 150                 155                 160
Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
                165                 170                 175
Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
            180                 185                 190
```

```
Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
        195                 200                 205
Val Ala Pro Thr Glu Ala
    210
```

<210> 123
<211> 212
<212> PRT
<213> Homo sapiens

<400> 123

```
Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
 1               5                  10                  15
Thr Ala Arg Ile Ser Cys Ser Gly Asp Ala Leu Gly Asp Lys Tyr Ala
            20                  25                  30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        35                  40                  45
Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50                  55                  60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65                  70                  75                  80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Arg Asp Pro Val Gly Phe Pro
                85                  90                  95
Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala
            100                 105                 110
Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala
        115                 120                 125
Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala
    130                 135                 140
Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val
145                 150                 155                 160
Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser
                165                 170                 175
Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr
            180                 185                 190
Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala
        195                 200                 205
Pro Thr Glu Ala
    210
```

<210> 124
<211> 214
<212> PRT
<213> Homo sapiens

<400> 124

```
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
```

```
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Leu Ser
                85                  90                  95
Pro Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
            100                 105                 110
Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
        115                 120                 125
Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
    130                 135                 140
Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
145                 150                 155                 160
Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
                165                 170                 175
Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
            180                 185                 190
Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
        195                 200                 205
Val Ala Pro Thr Glu Ala
    210

<210> 125
<211> 216
<212> PRT
<213> Homo sapiens

<400> 125
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Ser
                85                  90                  95
His Tyr Phe Phe Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110
Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
        115                 120                 125
Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
    130                 135                 140
Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
```

145 150 155 160
Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
165 170 175
Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
180 185 190
His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
195 200 205
Lys Thr Val Ala Pro Thr Glu Ala
210 215

<210> 126
<211> 212
<212> PRT
<213> Homo sapiens

<400> 126
Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15
Thr Ala Arg Ile Ser Cys Ser Gly Asp Ala Leu Gly Asp Lys Tyr Ala
20 25 30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45
Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Leu Arg Tyr Ser His
85 90 95
Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala
100 105 110
Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala
115 120 125
Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala
130 135 140
Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val
145 150 155 160
Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser
165 170 175
Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr
180 185 190
Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala
195 200 205
Pro Thr Glu Ala
210

<210> 127
<211> 214
<212> PRT
<213> Homo sapiens

<400> 127
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1   5   10   15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20   25   30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35   40   45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50   55   60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65   70   75   80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Leu Arg
                85   90   95
Asn Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
            100   105   110
Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
        115   120   125
Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
    130   135   140
Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
145   150   155   160
Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
                165   170   175
Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
            180   185   190
Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
        195   200   205
Val Ala Pro Thr Glu Ala
    210

<210> 128
<211> 215
<212> PRT
<213> Homo sapiens

<400> 128
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1   5   10   15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20   25   30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35   40   45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50   55   60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65   70   75   80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Thr
                85   90   95
Tyr Gly Ser Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100   105   110

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
115 120 125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
130 135 140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145 150 155 160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
165 170 175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
180 185 190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
195 200 205
Thr Val Ala Pro Thr Glu Ala
210 215

<210> 129
<211> 215
<212> PRT
<213> Homo sapiens

<400> 129
Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
50 55 60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65 70 75 80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Phe Asn Asp Ser Pro
85 90 95
Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
100 105 110
Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
115 120 125
Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
130 135 140
Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145 150 155 160
Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
165 170 175
Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
180 185 190
Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
195 200 205
Ser Phe Asn Arg Gly Glu Ala
210 215

<210> 130
<211> 215
<212> PRT
<213> Homo sapiens

<400> 130
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ile Ser
85 90 95
Gly Tyr Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
115 120 125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
130 135 140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145 150 155 160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
165 170 175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
180 185 190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
195 200 205
Thr Val Ala Pro Thr Glu Ala
210 215

<210> 131
<211> 216
<212> PRT
<213> Homo sapiens

<400> 131
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu

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65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Arg Asp Leu Tyr
                85                  90                  95
Tyr Val Tyr Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110
Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
        115                 120                 125
Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
    130                 135                 140
Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
145                 150                 155                 160
Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
                165                 170                 175
Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
            180                 185                 190
His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
        195                 200                 205
Lys Thr Val Ala Pro Thr Glu Ala
    210                 215

<210> 132
<211> 211
<212> PRT
<213> Homo sapiens

<400> 132
Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
 1              5                   10                  15
Thr Ala Arg Ile Ser Cys Ser Gly Asp Ala Leu Gly Asp Lys Tyr Ala
            20                  25                  30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        35                  40                  45
Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50                  55                  60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65                  70                  75                  80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Arg Ser Met Trp Val
                85                  90                  95
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
            100                 105                 110
Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
        115                 120                 125
Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
    130                 135                 140
Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
145                 150                 155                 160
Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
                165                 170                 175
Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
            180                 185                 190
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Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
        195                 200                 205
Thr Glu Ala
    210

<210> 133
<211> 215
<212> PRT
<213> Homo sapiens

<400> 133
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp Val Gln
                85                  90                  95
Thr Asp Lys Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145                 150                 155                 160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205
Thr Val Ala Pro Thr Glu Ala
    210                 215

<210> 134
<211> 212
<212> PRT
<213> Homo sapiens

<400> 134
Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
 1               5                  10                  15
Thr Ala Arg Ile Ser Cys Ser Gly Asp Ala Leu Gly Asp Lys Tyr Ala
            20                  25                  30
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Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        35                  40                  45
Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50                  55                  60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65                  70                  75                  80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp Pro Ser His Tyr Tyr
                85                  90                  95
Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala
            100                 105                 110
Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala
        115                 120                 125
Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala
    130                 135                 140
Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val
145                 150                 155                 160
Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser
                165                 170                 175
Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr
            180                 185                 190
Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala
        195                 200                 205
Pro Thr Glu Ala
    210

<210> 135
<211> 215
<212> PRT
<213> Homo sapiens

<400> 135
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ile Met
                85                  90                  95
Pro Glu Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
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145 150 155 160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
165 170 175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
180 185 190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
195 200 205
Thr Val Ala Pro Thr Glu Ala
210 215

<210> 136
<211> 215
<212> PRT
<213> Homo sapiens

<400> 136
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Met Asp Phe Arg
85 90 95
Leu Met His Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
115 120 125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
130 135 140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145 150 155 160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
165 170 175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
180 185 190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
195 200 205
Thr Val Ala Pro Thr Glu Ala
210 215

<210> 137
<211> 215
<212> PRT
<213> Homo sapiens

<400> 137
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Phe Asp Met Ile
85 90 95
His Pro Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
115 120 125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
130 135 140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145 150 155 160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
165 170 175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
180 185 190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
195 200 205
Thr Val Ala Pro Thr Glu Ala
210 215

<210> 138
<211> 213
<212> PRT
<213> Homo sapiens

<400> 138
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Asp Phe Pro Val
85 90 95
Met Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125
Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140
Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160
Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175
Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190
Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205
Ala Pro Thr Glu Ala
210

<210> 139
<211> 213
<212> PRT
<213> Homo sapiens

<400> 139
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Asp Asn Pro Tyr
85 90 95
Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110
Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125
Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140
Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160
Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175
Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190
Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205
Ala Pro Thr Glu Ala
210

<210> 140
<211> 217
<212> PRT
<213> Homo sapiens

<400> 140
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Phe Met Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser
100 105 110
Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
115 120 125
Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
130 135 140
Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145 150 155 160
Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
165 170 175
Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
180 185 190
Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
195 200 205
Lys Lys Val Glu Pro Lys Ser Glu Phe
210 215

<210> 141
<211> 217
<212> PRT
<213> Homo sapiens

<400> 141
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

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65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Gly Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
            100                 105                 110
Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
        115                 120                 125
Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
    130                 135                 140
Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145                 150                 155                 160
Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
                165                 170                 175
Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
            180                 185                 190
Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
        195                 200                 205
Lys Lys Val Glu Pro Lys Ser Glu Phe
    210                 215

<210> 142
<211> 217
<212> PRT
<213> Homo sapiens

<400> 142
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Phe Leu Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser
            100                 105                 110
Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
        115                 120                 125
Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
    130                 135                 140
Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145                 150                 155                 160
Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
                165                 170                 175
Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
            180                 185                 190
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Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
        195                 200                 205
Lys Lys Val Glu Pro Lys Ser Glu Phe
    210                 215

<210> 143
<211> 221
<212> PRT
<213> Homo sapiens

<400> 143
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Thr Phe Pro Ile Asp Ala Asp Ser Trp Gly Gln Gly Thr Leu
            100                 105                 110
Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
        115                 120                 125
Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
    130                 135                 140
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175
Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
            180                 185                 190
Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
        195                 200                 205
Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
    210                 215                 220

<210> 144
<211> 218
<212> PRT
<213> Homo sapiens

<400> 144
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30
```

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Gly His Val Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
100 105 110
Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser
115 120 125
Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys
130 135 140
Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu
145 150 155 160
Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu
165 170 175
Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr
180 185 190
Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val
195 200 205
Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
210 215

<210> 145
<211> 222
<212> PRT
<213> Homo sapiens

<400> 145
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Tyr Trp Arg Gly Leu Ser Phe Asp Ile Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
115 120 125
Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
130 135 140
Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn

145 150 155 160
Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
165 170 175
Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
180 185 190
Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
195 200 205
Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
210 215 220

<210> 146
<211> 217
<212> PRT
<213> Homo sapiens

<400> 146
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Phe Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
100 105 110
Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
115 120 125
Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
130 135 140
Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145 150 155 160
Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
165 170 175
Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
180 185 190
Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
195 200 205
Lys Lys Val Glu Pro Lys Ser Glu Phe
210 215

<210> 147
<211> 225
<212> PRT
<213> Homo sapiens

<400> 147
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
20 25 30
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Gly Leu Tyr Trp Ala Val Tyr Pro Tyr Phe Asp Phe Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
130 135 140
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
195 200 205
Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu
210 215 220
Phe
225

<210> 148
<211> 224
<212> PRT
<213> Homo sapiens

<400> 148
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

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Ala Arg Leu Asp Thr Tyr Tyr Pro Asp Leu Phe Asp Tyr Trp Gly Gln
            100                 105                 110
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
    210                 215                 220

<210> 149
<211> 220
<212> PRT
<213> Homo sapiens

<400> 149
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1               5                  10                  15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
            20                  25                  30
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
    50                  55                  60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Thr Tyr Tyr Tyr Phe Asp Ser Trp Gly Gln Gly Thr Leu Val
            100                 105                 110
Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
        115                 120                 125
Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
    130                 135                 140
Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145                 150                 155                 160
Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
                165                 170                 175
Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
            180                 185                 190
Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
        195                 200                 205
Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
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    210                 215                 220

<210> 150
<211> 224
<212> PRT
<213> Homo sapiens

<400> 150
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Tyr Met Ala Tyr Met Ala Glu Ala Ile Asp Val Trp Gly Gln
            100                 105                 110
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
    210                 215                 220

<210> 151
<211> 230
<212> PRT
<213> Homo sapiens

<400> 151
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1               5                  10                  15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe
```

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    50                  55                  60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Leu Val Gly Ile Val Gly Tyr Lys Pro Asp Glu Leu Leu Tyr
            100                 105                 110
Phe Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
        115                 120                 125
Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
    130                 135                 140
Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
145                 150                 155                 160
Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
                165                 170                 175
His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
            180                 185                 190
Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
        195                 200                 205
Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
    210                 215                 220
Glu Pro Lys Ser Glu Phe
225                 230
```

<210> 152
<211> 222
<212> PRT
<213> Homo sapiens

<400> 152

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Tyr Gly Ala Tyr Phe Gly Leu Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110
Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        115                 120                 125
Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    130                 135                 140
Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145                 150                 155                 160
```

```
Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                165                 170                 175
Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            180                 185                 190
Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        195                 200                 205
Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
    210                 215                 220

<210> 153
<211> 225
<212> PRT
<213> Homo sapiens

<400> 153
Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
 1               5                  10                  15
Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
            20                  25                  30
Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Gly Arg Gly Leu Glu
        35                  40                  45
Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
    50                  55                  60
Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
65                  70                  75                  80
Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
                85                  90                  95
Tyr Tyr Cys Ala Arg Gly Tyr Ala Asp Ile Ser Phe Asp Tyr Trp Gly
            100                 105                 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
        115                 120                 125
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
    130                 135                 140
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145                 150                 155                 160
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
        195                 200                 205
Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu
    210                 215                 220
Phe
225

<210> 154
<211> 220
<212> PRT
<213> Homo sapiens
```

<400> 154
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Tyr Tyr Leu Leu Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125
Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140
Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160
Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175
Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190
Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205
Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
210 215 220

<210> 155
<211> 229
<212> PRT
<213> Homo sapiens

<400> 155
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
20 25 30
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Trp Ser Asp Gln Ser Tyr His Tyr Tyr Trp His Pro Tyr Phe

```
            100                         105                         110
Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr
        115                         120                         125
Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
    130                         135                         140
Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145                         150                         155                         160
Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
                165                         170                         175
Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
            180                         185                         190
Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
        195                         200                         205
Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
    210                         215                         220
Pro Lys Ser Glu Phe
225

<210> 156
<211> 220
<212> PRT
<213> Homo sapiens

<400> 156
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Leu Ile Gly Tyr Phe Asp Leu Trp Gly Gln Gly Thr Leu Val
            100                 105                 110
Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
        115                 120                 125
Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
    130                 135                 140
Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145                 150                 155                 160
Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
                165                 170                 175
Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
            180                 185                 190
Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
        195                 200                 205
```

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
210 215 220

<210> 157
<211> 225
<212> PRT
<213> Homo sapiens

<400> 157
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Leu Thr Asn Tyr Phe Asp Ser Ile Tyr Tyr Asp His Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
130 135 140
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
195 200 205
Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu
210 215 220
Phe
225

<210> 158
<211> 225
<212> PRT
<213> Homo sapiens

<400> 158
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

```
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95
Ala Arg Leu Val Gly Gly Gly Tyr Asp Leu Met Phe Asp Ser Trp Gly
            100                 105                 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
        115                 120                 125
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
    130                 135                 140
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145                 150                 155                 160
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
        195                 200                 205
Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu
    210                 215                 220
Phe
225

<210> 159
<211> 226
<212> PRT
<213> Homo sapiens

<400> 159
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1               5                  10                  15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
            20                  25                  30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95
Ala Arg Tyr Val Thr Tyr Gly Tyr Asp Asp Tyr His Phe Asp Tyr Trp
            100                 105                 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125
Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
```

```
    130                 135                 140
Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160
Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175
Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190
Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
        195                 200                 205
His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
    210                 215                 220
Glu Phe
225
```

<210> 160
<211> 219
<212> PRT
<213> Homo sapiens

<400> 160

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1               5                  10                  15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
            20                  25                  30
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
    50                  55                  60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Ser Gly Tyr Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110
Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
        115                 120                 125
Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
    130                 135                 140
Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
145                 150                 155                 160
Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
                165                 170                 175
Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
            180                 185                 190
Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
        195                 200                 205
Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
    210                 215
```

<210> 161

<211> 231
<212> PRT
<213> Homo sapiens

<400> 161
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
20 25 30
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Tyr Ile Gly Tyr Thr Asn Val Met Asp Ile Arg Pro Gly Phe
100 105 110
Tyr Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
115 120 125
Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
130 135 140
Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
145 150 155 160
Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
165 170 175
Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
180 185 190
Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
195 200 205
Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys
210 215 220
Val Glu Pro Lys Ser Glu Phe
225 230

<210> 162
<211> 225
<212> PRT
<213> Homo sapiens

<400> 162
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Phe Arg Ala Tyr Gly Asp Asp Phe Tyr Phe Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
130 135 140
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
195 200 205
Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu
210 215 220
Phe
225

<210> 163
<211> 228
<212> PRT
<213> Homo sapiens

<400> 163
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ile Met Trp Ser Asp Tyr Gly Gln Leu Val Lys Gly Gly Asp
100 105 110
Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys
115 120 125
Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly
130 135 140
Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
145 150 155 160
Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr

```
                165                     170                     175
Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
            180                     185                     190
Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn
        195                     200                     205
Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro
    210                     215                     220
Lys Ser Glu Phe
225
```

<210> 164
<211> 224
<212> PRT
<213> Homo sapiens

<400> 164

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1               5                  10                  15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
            20                  25                  30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95
Ala Arg Tyr Tyr Val Thr Asp Thr Ala Tyr Phe Asp Tyr Trp Gly Gln
            100                 105                 110
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
    210                 215                 220
```

<210> 165
<211> 224
<212> PRT
<213> Homo sapiens

<400> 165
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1   5   10   15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
            20   25   30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35   40   45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50   55   60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65   70   75   80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85   90   95
Ala Arg His Asp Phe Asp Gly Ser Ile Phe Met Asp Phe Trp Gly Gln
            100   105   110
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115   120   125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130   135   140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145   150   155   160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165   170   175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180   185   190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195   200   205
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
    210   215   220

<210> 166
<211> 225
<212> PRT
<213> Homo sapiens

<400> 166
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1   5   10   15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
            20   25   30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35   40   45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50   55   60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65   70   75   80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85   90   95
Ala Arg Tyr Ala Gly His Gln Tyr Glu Phe Phe Phe Asp Phe Trp Gly
            100   105   110

```
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
        115                 120                 125
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
    130                 135                 140
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145                 150                 155                 160
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
        195                 200                 205
Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu
    210                 215                 220
Phe
225

<210> 167
<211> 224
<212> PRT
<213> Homo sapiens

<400> 167
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1               5                  10                  15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
            20                  25                  30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95
Ala Arg Leu Tyr Ala Asp Ala Asp Ile Tyr Phe Asp Tyr Trp Gly Gln
            100                 105                 110
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
```

210 215 220

<210> 168
<211> 222
<212> PRT
<213> Homo sapiens

<400> 168
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
20 25 30
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Thr Lys Tyr Val Gly Ser Glu Asp Val Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
115 120 125
Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
130 135 140
Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145 150 155 160
Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
165 170 175
Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
180 185 190
Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
195 200 205
Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
210 215 220

<210> 169
<211> 222
<212> PRT
<213> Homo sapiens

<400> 169
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe

```
    50                  55                  60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95
Ala Arg Tyr Arg Tyr Pro His Met Phe Asp Phe Trp Gly Gln Gly Thr
            100                 105                 110
Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        115                 120                 125
Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    130                 135                 140
Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145                 150                 155                 160
Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                165                 170                 175
Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            180                 185                 190
Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        195                 200                 205
Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
    210                 215                 220

<210> 170
<211> 224
<212> PRT
<213> Homo sapiens

<400> 170
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1               5                  10                  15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
            20                  25                  30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95
Ala Arg Leu Phe Ala Gly Leu Glu Leu Tyr Phe Asp Tyr Trp Gly Gln
            100                 105                 110
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175
```

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
210 215 220

<210> 171
<211> 221
<212> PRT
<213> Homo sapiens

<400> 171
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Gly Gly Phe Phe Asn Met Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125
Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175
Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190
Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205
Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
210 215 220

<210> 172
<211> 223
<212> PRT
<213> Homo sapiens

<400> 172
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

```
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
            20                  25                  30
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
    50                  55                  60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Gly Tyr Ile Pro Tyr His Leu Phe Asp Tyr Trp Gly Gln Gly
            100                 105                 110
Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
        115                 120                 125
Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
    130                 135                 140
Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145                 150                 155                 160
Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175
Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
            180                 185                 190
Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
        195                 200                 205
Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
    210                 215                 220

<210> 173
<211> 225
<212> PRT
<213> Homo sapiens

<400> 173
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1               5                   10                  15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
            20                  25                  30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95
Ala Arg Tyr Tyr Gly Phe Glu Tyr Asp Leu Leu Phe Asp Asn Trp Gly
            100                 105                 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
        115                 120                 125
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
```

130 135 140
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
195 200 205
Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu
210 215 220
Phe
225

<210> 174
<211> 221
<212> PRT
<213> Homo sapiens

<400> 174
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
20 25 30
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ile Thr Tyr Ile Gly Tyr Asp Phe Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125
Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175
Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190
Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205
Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
210 215 220

<210> 175

<211> 220
<212> PRT
<213> Homo sapiens

<400> 175
```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1               5                  10                  15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
            20                  25                  30
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
    50                  55                  60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Gln Glu Trp Tyr Met Asp Tyr Trp Gly Gln Gly Thr Leu Val
            100                 105                 110
Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
        115                 120                 125
Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
    130                 135                 140
Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145                 150                 155                 160
Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
                165                 170                 175
Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
            180                 185                 190
Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
        195                 200                 205
Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
    210                 215                 220
```

<210> 176
<211> 224
<212> PRT
<213> Homo sapiens

<400> 176
```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1               5                  10                  15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
            20                  25                  30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
```

```
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95
Ala Arg Leu Tyr Pro Glu Asp Leu Ile Tyr Phe Asp Tyr Trp Gly Gln
            100                 105                 110
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
    210                 215                 220

<210> 177
<211> 231
<212> PRT
<213> Homo sapiens

<400> 177
Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
 1               5                  10                  15
Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
            20                  25                  30
Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Gly Arg Gly Leu Glu
        35                  40                  45
Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
    50                  55                  60
Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
65                  70                  75                  80
Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
                85                  90                  95
Tyr Tyr Cys Ala Arg Trp Met Thr Pro Pro Gly His Tyr Tyr Gly Tyr
            100                 105                 110
Thr Phe Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
        115                 120                 125
Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
    130                 135                 140
Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
145                 150                 155                 160
Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
                165                 170                 175
Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
            180                 185                 190
Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
```

```
        195                 200                 205
Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys
    210                 215                 220
Val Glu Pro Lys Ser Glu Phe
225                 230

<210> 178
<211> 225
<212> PRT
<213> Homo sapiens

<400> 178
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1               5                  10                  15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
            20                  25                  30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95
Ala Arg Leu Arg Val His Asp Tyr Ala Met Tyr Phe Asp Leu Trp Gly
            100                 105                 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
        115                 120                 125
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
    130                 135                 140
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145                 150                 155                 160
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
        195                 200                 205
Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu
    210                 215                 220
Phe
225

<210> 179
<211> 226
<212> PRT
<213> Homo sapiens

<400> 179
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
```

```
 1               5                   10                  15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
            20                  25                  30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95
Ala Arg Phe Val Ser Tyr Asn Gly Ser Val Pro Tyr Phe Asp Tyr Trp
            100                 105                 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125
Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
    130                 135                 140
Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160
Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175
Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190
Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
        195                 200                 205
His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
    210                 215                 220
Glu Phe
225
```

<210> 180
<211> 224
<212> PRT
<213> Homo sapiens

<400> 180

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1               5                   10                  15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
            20                  25                  30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95
Ala Arg Ile Ile Gly Asp Tyr Val Ile Phe Phe Asp Val Trp Gly Gln
            100                 105                 110
```

```
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
    210                 215                 220

<210> 181
<211> 224
<212> PRT
<213> Homo sapiens

<400> 181
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1               5                  10                  15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
            20                  25                  30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95
Ala Arg Leu Phe Thr Tyr Pro Phe Leu Tyr Phe Asp Val Trp Gly Gln
            100                 105                 110
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
    210                 215                 220
```

<210> 182
<211> 224
<212> PRT
<213> Homo sapiens

<400> 182
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Ile Leu Thr Gly His Val Leu Leu Phe Asp Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
210 215 220

<210> 183
<211> 27
<212> DNA
<213> Homo sapiens

<400> 183
cagagctatg actatcagca gtttact 27

<210> 184
<211> 26
<212> DNA
<213> Homo sapiens

<400> 184
cagagctatg actttaagac ttatct 26

<210> 185
<211> 26
<212> DNA
<213> Homo sapiens

<400> 185
cagagctatg actttcttcg tttttc 26

<210> 186
<211> 27
<212> DNA
<213> Homo sapiens

<400> 186
cagagctatg actttattaa tgttatt 27

<210> 187
<211> 27
<212> DNA
<213> Homo sapiens

<400> 187
cagagctatg actttgttcg ttttatg 27

<210> 188
<211> 27
<212> DNA
<213> Homo sapiens

<400> 188
cagagctatg acttttataa gtttaat 27

<210> 189
<211> 27
<212> DNA
<213> Homo sapiens

<400> 189
cagagctatg actttcgtcg tttttct 27

<210> 190
<211> 27
<212> DNA
<213> Homo sapiens

<400> 190
cagagccgtg actttaatcg tggtcct 27

<210> 191

<211> 24
<212> DNA
<213> Homo sapiens

<400> 191
cagagctatg accagcgtaa gtgg 24

<210> 192
<211> 24
<212> DNA
<213> Homo sapiens

<400> 192
cagcagcttt atggtacttc tgtt 24

<210> 193
<211> 27
<212> DNA
<213> Homo sapiens

<400> 193
cagagctatg acggttttaa gactcat 27

<210> 194
<211> 24
<212> DNA
<213> Homo sapiens

<400> 194
cagagctatg actattctct tctt 24

<210> 195
<211> 24
<212> DNA
<213> Homo sapiens

<400> 195
cagagctatg actttaattt tcat 24

<210> 196
<211> 30
<212> DNA
<213> Homo sapiens

<400> 196
cagagctatg acatgattgc tcgttatcct 30

<210> 197
<211> 30
<212> DNA

<213> Homo sapiens

<400> 197
cagagctggg acattcatcc ttttgatgtt 30

<210> 198
<211> 24
<212> DNA
<213> Homo sapiens

<400> 198
cagagctggg accttgagcc ttat 24

<210> 199
<211> 27
<212> DNA
<213> Homo sapiens

<400> 199
cagagctatg acgttcttga ttctgag 27

<210> 200
<211> 30
<212> DNA
<213> Homo sapiens

<400> 200
cagagctatg acccttctca tccttctaag 30

<210> 201
<211> 24
<212> DNA
<213> Homo sapiens

<400> 201
cagagctatg acgatatgca gttt 24

<210> 202
<211> 27
<212> DNA
<213> Homo sapiens

<400> 202
cagagctggg acattaatca tgctatt 27

<210> 203
<211> 27
<212> DNA
<213> Homo sapiens

<400> 203
cagagctatg actattatga ttatggt 27

<210> 204
<211> 24
<212> DNA
<213> Homo sapiens

<400> 204
cagcaggcta atgattttcc tatt 24

<210> 205
<211> 30
<212> DNA
<213> Homo sapiens

<400> 205
cagagctggg acaatcttaa gatgcctgtt 30

<210> 206
<211> 30
<212> DNA
<213> Homo sapiens

<400> 206
cagagctatg acgtttttcc tattaatcgt 30

<210> 207
<211> 21
<212> DNA
<213> Homo sapiens

<400> 207
cagagcgatc tttattttcc t 21

<210> 208
<211> 24
<212> DNA
<213> Homo sapiens

<400> 208
cagagctatg acgttactcc tcgt 24

<210> 209
<211> 27
<212> DNA
<213> Homo sapiens

<400> 209
cagagccgtg accctgttgg ttttcct 27

<210> 210
<211> 24
<212> DNA
<213> Homo sapiens

<400> 210
cagagctatg acctttctcc tcgt 24

<210> 211
<211> 30
<212> DNA
<213> Homo sapiens

<400> 211
cagagctatg acttttctca ttattttttt 30

<210> 212
<211> 27
<212> DNA
<213> Homo sapiens

<400> 212
cagagctatg accttcgtta ttctcat 27

<210> 213
<211> 24
<212> DNA
<213> Homo sapiens

<400> 213
cagagctatg accttcgtaa tcgt 24

<210> 214
<211> 27
<212> DNA
<213> Homo sapiens

<400> 214
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<211> 669
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<212> DNA
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gcttattttg gtcttgatta ttggggccaa ggcaccctgg tgacggttag ctcagcgtcg 360
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agcggggcgc tgaccagcgg cgtgcatacc tttccggcgg tgctgcaaag cagcggcctg 540
tatagcctga gcagcgttgt gaccgtgccg agcagcagct taggcactca gacctatatt 600
tgcaacgtga accataaacc gagcaacacc aaagtggata aaaaagtgga accgaaaagc 660

<210> 282
<211> 669
<212> DNA
<213> Homo sapiens

<400> 282
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acctgtgcga tttccggaga tagcgtgagc agcaacagcg cggcgtggaa ctggattcgc 120
cagtctcctg ggcgtggcct cgagtggctg ggccgtacct attatcgtag caaatggtat 180
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cagtttagcc tgcaactgaa cagcgtgacc ccggaagata cggccgtgta ttattgcgcg 300
cgtggttatg ctgatatttc ttttgattat tggggccaag gcaccctggt gacggttagc 360
tcagcgtcga ccaaaggtcc aagcgtgttt ccgctggctc cgagcagcaa aagcaccagc 420
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agctggaaca gcggggcgct gaccagcggc gtgcatacct ttccggcggt gctgcaaagc 540
agcggcctgt atagcctgag cagcgttgtg accgtgccga gcagcagctt aggcactcag 600
acctatattt gcaacgtgaa ccataaaccg agcaacacca aagtggataa aaaagtggaa 660
ccgaaaagc 669

<210> 283
<211> 654
<212> DNA
<213> Homo sapiens

<400> 283
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agctgcgcgg cctccggatt tacctttagc agctatgcga tgagctgggt gcgccaagcc 120
cctgggaagg gtctcgagtg ggtgagcgcg attagcggta gcggcggcag cacctattat 180
gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240
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ctgagcagcg ttgtgaccgt gccgagcagc agcttaggca ctcagaccta tatttgcaac 600
gtgaaccata aaccgagcaa caccaaagtg gataaaaaag tggaaccgaa aagc 654

<210> 284
<211> 681

<212> DNA
<213> Homo sapiens

<400> 284
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agctgcaaag cctccggagg cacttttagc agctatgcga ttagctgggt gcgccaagcc 120
cctgggcagg gtctcgagtg gatgggcggc attattccga tttttggcac ggcgaactac 180
gcgcagaagt ttcagggccg ggtgaccatt accgcggatg aaagcaccag caccgcgtat 240
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gatcagtctt atcattatta ttggcatcct tattttgatg tttggggcca aggcaccctg 360
gtgacggtta gctcagcgtc gaccaaaggt ccaagcgtgt ttccgctggc tccgagcagc 420
aaaagcacca gcggcggcac ggctgccctg ggctgcctgg ttaaagatta tttcccggaa 480
ccagtcaccg tgagctggaa cagcggggcg ctgaccagcg gcgtgcatac ctttccggcg 540
gtgctgcaaa gcagcggcct gtatagcctg agcagcgttg tgaccgtgcc gagcagcagc 600
ttaggcactc agacctatat ttgcaacgtg aaccataaac cgagcaacac caaagtggat 660
aaaaaagtgg aaccgaaaag c 681

<210> 285
<211> 654
<212> DNA
<213> Homo sapiens

<400> 285
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agctgcgcgg cctccggatt tacctttagc agctatgcga tgagctgggt gcgccaagcc 120
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gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240
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ggttattttg atctttgggg ccaaggcacc ctggtgacgg ttagctcagc gtcgaccaaa 360
ggtccaagcg tgtttccgct ggctccgagc agcaaaagca ccagcggcgg cacggctgcc 420
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gtgaaccata aaccgagcaa caccaaagtg gataaaaaag tggaaccgaa aagc 654

<210> 286
<211> 669
<212> DNA
<213> Homo sapiens

<400> 286
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agctgcaaag gttccggata ttcctttacg agctattgga ttggctgggt gcgccagatg 120
cctgggaagg gtctcgagtg gatgggcatt atttatccgg gcgatagcga tacccgttat 180
tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240
cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgtcttact 300
aattattttg attctattta ttatgatcat tggggccaag gcaccctggt gacggttagc 360
tcagcgtcga ccaaaggtcc aagcgtgttt ccgctggctc cgagcagcaa aagcaccagc 420
ggcggcacgg ctgccctggg ctgcctggtt aaagattatt tcccggaacc agtcaccgtg 480
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agcggcctgt atagcctgag cagcgttgtg accgtgccga gcagcagctt aggcactcag 600
acctatattt gcaacgtgaa ccataaaccg agcaacacca aagtggataa aaaagtggaa 660
ccgaaaagc 669

<210> 287
<211> 669
<212> DNA
<213> Homo sapiens

<400> 287
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agctgcaaag gttccggata ttcctttacg agctattgga ttggctgggt gcgccagatg 120
cctgggaagg gtctcgagtg gatgggcatt atttatccgg gcgatagcga tacccgttat 180
tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240
cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgtcttgtt 300
ggtggtggtt atgatcttat gtttgattct tggggccaag gcaccctggt gacggttagc 360
tcagcgtcga ccaaaggtcc aagcgtgttt ccgctggctc cgagcagcaa aagcaccagc 420
ggcggcacgg ctgccctggg ctgcctggtt aaagattatt tcccggaacc agtcaccgtg 480
agctggaaca gcggggcgct gaccagcggc gtgcatacct ttccggcggt gctgcaaagc 540
agcggcctgt atagcctgag cagcgttgtg accgtgccga gcagcagctt aggcactcag 600
acctatattt gcaacgtgaa ccataaaccg agcaacacca aagtggataa aaaagtggaa 660
ccgaaaagc 669

<210> 288
<211> 672
<212> DNA
<213> Homo sapiens

<400> 288
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agctgcaaag gttccggata ttcctttacg agctattgga ttggctgggt gcgccagatg 120
cctgggaagg gtctcgagtg gatgggcatt atttatccgg gcgatagcga tacccgttat 180
tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240
cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttatgtt 300
acttatggtt atgatgatta tcattttgat tattggggcc aaggcaccct ggtgacggtt 360
agctcagcgt cgaccaaagg tccaagcgtg tttccgctgg ctccgagcag caaaagcacc 420
agcggcggca cggctgccct gggctgcctg gttaaagatt atttcccgga accagtcacc 480
gtgagctgga acagcggggc gctgaccagc ggcgtgcata cctttccggc ggtgctgcaa 540
agcagcggcc tgtatagcct gagcagcgtt gtgaccgtgc cgagcagcag cttaggcact 600
cagacctata tttgcaacgt gaaccataaa ccgagcaaca ccaaagtgga taaaaaagtg 660
gaaccgaaaa gc 672

<210> 289
<211> 651
<212> DNA
<213> Homo sapiens

<400> 289
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agctgcaaag cctccggagg cacttttagc agctatgcga ttagctgggt gcgccaagcc 120

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cctgggcagg gtctcgagtg gatgggcggc attattccga tttttggcac ggcgaactac      180
gcgcagaagt ttcagggccg ggtgaccatt accgcggatg aaagcaccag caccgcgtat      240
atggaactga gcagcctgcg tagcgaagat acggccgtgt attattgcgc gcgttctggt      300
tatcttgatt attggggcca aggcaccctg gtgacggtta gctcagcgtc gaccaaaggt      360
ccaagcgtgt ttccgctggc tccgagcagc aaaagcacca gcggcggcac ggctgccctg      420
ggctgcctgg ttaaagatta tttcccggaa ccagtcaccg tgagctggaa cagcggggcg      480
ctgaccagcg gcgtgcatac ctttccggcg gtgctgcaaa gcagcggcct gtatagcctg      540
agcagcgttg tgaccgtgcc gagcagcagc ttaggcactc agacctatat ttgcaacgtg      600
aaccataaac cgagcaacac caaagtggat aaaaaagtgg aaccgaaaag c               651

&lt;210&gt; 290
&lt;211&gt; 687
&lt;212&gt; DNA
&lt;213&gt; Homo sapiens

&lt;400&gt; 290
caggtgcaat tggttcagtc tggcgcggaa gtgaaaaaac cgggcagcag cgtgaaagtg       60
agctgcaaag cctccggagg cacttttagc agctatgcga ttagctgggt gcgccaagcc      120
cctgggcagg gtctcgagtg gatgggcggc attattccga tttttggcac ggcgaactac      180
gcgcagaagt ttcagggccg ggtgaccatt accgcggatg aaagcaccag caccgcgtat      240
atggaactga gcagcctgcg tagcgaagat acggccgtgt attattgcgc gcgttatatt      300
ggttatacta atgttatgga tattcgtcct ggtttttatc ttgattattg gggccaaggc      360
accctggtga cggttagctc agcgtcgacc aaaggtccaa gcgtgtttcc gctggctccg      420
agcagcaaaa gcaccagcgg cggcacggct gccctgggct gcctggttaa agattatttc      480
ccggaaccag tcaccgtgag ctggaacagc ggggcgctga ccagcggcgt gcatacsttt      540
ccggcggtgc tgcaaagcag cggcctgtat agcctgagca gcgttgtgac cgtgccgagc      600
agcagcttag gcactcagac ctatatttgc aacgtgaacc ataaaccgag caacaccaaa      660
gtggataaaa aagtggaacc gaaaagc                                          687

&lt;210&gt; 291
&lt;211&gt; 669
&lt;212&gt; DNA
&lt;213&gt; Homo sapiens

&lt;400&gt; 291
caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt       60
agctgcaaag gttccggata ttcctttacg agctattgga ttggctgggt gcgccagatg      120
cctgggaagg gtctcgagtg gatgggcatt atttatccgg gcgatagcga tacccgttat      180
tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat      240
cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttttcgt      300
gcttatggtg atgattttta ttttgatgtt tggggccaag gcaccctggt gacggttagc      360
tcagcgtcga ccaaaggtcc aagcgtgttt ccgctggctc cgagcagcaa aagcaccagc      420
ggcggcacgg ctgccctggg ctgcctggtt aaagattatt tcccggaacc agtcaccgtg      480
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agcggcctgt atagcctgag cagcgttgtg accgtgccga gcagcagctt aggcactcag      600
acctatattt gcaacgtgaa ccataaaccg agcaacacca aagtggataa aaaagtggaa      660
ccgaaaagc                                                              669

&lt;210&gt; 292
&lt;211&gt; 678
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<212> DNA
<213> Homo sapiens

<400> 292
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cctgggcagg gtctcgagtg gatgggctgg attaacccga atagcggcgg cacgaactac 180
gcgcagaagt ttcagggccg ggtgaccatg acccgtgata ccagcattag caccgcgtat 240
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tggtctgatt atggtcagct tgttaagggt ggtgatattt ggggccaagg caccctggtg 360
acggttagct cagcgtcgac caaaggtcca agcgtgtttc cgctggctcc gagcagcaaa 420
agcaccagcg gcggcacggc tgccctgggc tgcctggtta aagattattt cccggaacca 480
gtcaccgtga gctggaacag cggggcgctg accagcggcg tgcatacctt tccggcggtg 540
ctgcaaagca gcggcctgta tagcctgagc agcgttgtga ccgtgccgag cagcagctta 600
ggcactcaga cctatatttg caacgtgaac cataaaccga gcaacaccaa agtggataaa 660
aaagtggaac cgaaaagc 678

<210> 293
<211> 666
<212> DNA
<213> Homo sapiens

<400> 293
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cctgggaagg gtctcgagtg gatgggcatt atttatccgg gcgatagcga tacccgttat 180
tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240
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gttactgata ctgcttattt tgattattgg ggccaaggca ccctggtgac ggttagctca 360
gcgtcgacca aaggtccaag cgtgtttccg ctggctccga gcagcaaaag caccagcggc 420
ggcacggctg ccctgggctg cctggttaaa gattatttcc cggaaccagt caccgtgagc 480
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ggcctgtata gcctgagcag cgttgtgacc gtgccgagca gcagcttagg cactcagacc 600
tatatttgca acgtgaacca taaaccgagc aacaccaaag tggataaaaa agtggaaccg 660
aaaagc 666

<210> 294
<211> 666
<212> DNA
<213> Homo sapiens

<400> 294
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agctgcaaag gttccggata ttcctttacg agctattgga ttggctgggt gcgccagatg 120
cctgggaagg gtctcgagtg gatgggcatt atttatccgg gcgatagcga tacccgttat 180
tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240
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tttgatggtt ctatttttat ggatttttgg ggccaaggca ccctggtgac ggttagctca 360
gcgtcgacca aaggtccaag cgtgtttccg ctggctccga gcagcaaaag caccagcggc 420
ggcacggctg ccctgggctg cctggttaaa gattatttcc cggaaccagt caccgtgagc 480

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tggaacagcg gggcgctgac cagcggcgtg catacctttc cggcggtgct gcaaagcagc     540
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tatatttgca acgtgaacca taaaccgagc aacaccaaag tggataaaaa agtggaaccg     660
aaaagc                                                                666
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<210> 295
<211> 669
<212> DNA
<213> Homo sapiens

<400> 295

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cctgggaagg gtctcgagtg gatgggcatt atttatccgg gcgatagcga tacccgttat     180
tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat     240
cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttatgct     300
ggtcatcagt atgagttttt ttttgatttt tggggccaag gcaccctggt gacggttagc     360
tcagcgtcga ccaaaggtcc aagcgtgttt ccgctggctc cgagcagcaa aagcaccagc     420
ggcggcacgg ctgccctggg ctgcctggtt aaagattatt tcccggaacc agtcaccgtg     480
agctggaaca gcggggcgct gaccagcggc gtgcatacct ttccggcggt gctgcaaagc     540
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ccgaaaagc                                                             669
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<210> 296
<211> 614
<212> DNA
<213> Homo sapiens

<400> 296

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cccgttattc tccgagcttt cagggccagg tgaccattag cgcggataaa agcattagca     180
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gtctttatgc tgatgctgat atttattttg attattgggg ccaaggcacc ctggtgacgg     300
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ccagcggcgg cacggctgcc ctgggctgcc tggttaaaga ttatttcccg gaaccagtca     420
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aaagcagcgg cctgtatagc ctgagcagcg ttgtgaccgt gccgagcagc agcttaggca     540
ctcagaccta tatttgcaac gtgaaccata aaccgagcaa caccaaagtg gataaaaaag     600
tggaaccgaa aagc                                                       614
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<210> 297
<211> 660
<212> DNA
<213> Homo sapiens

<400> 297

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agctgcaaag cctccggagg cacttttagc agctatgcga ttagctgggt gcgccaagcc     120
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cctgggcagg gtctcgagtg gatgggcggc attattccga tttttggcac ggcgaactac      180
gcgcagaagt ttcagggccg ggtgaccatt accgcggatg aaagcaccag caccgcgtat      240
atggaactga gcagcctgcg tagcgaagat acggccgtgt attattgcgc gcgtactaag      300
tatgttggtt ctgaggatgt ttggggccaa ggcaccctgg tgacggttag ctcagcgtcg      360
accaaaggtc caagcgtgtt tccgctggct ccgagcagca aaagcaccag cggcggcacg      420
gctgccctgg gctgcctggt taaagattat ttcccggaac cagtcaccgt gagctggaac      480
agcggggcgc tgaccagcgg cgtgcatacc tttccggcgg tgctgcaaag cagcggcctg      540
tatagcctga gcagcgttgt gaccgtgccg agcagcagct taggcactca gacctatatt      600
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<210> 298
<211> 660
<212> DNA
<213> Homo sapiens

<400> 298

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agctgcaaag gttccggata ttcctttacg agctattgga ttggctgggt gcgccagatg      120
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cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttatcgt      300
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accaaaggtc caagcgtgtt tccgctggct ccgagcagca aaagcaccag cggcggcacg      420
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agcggggcgc tgaccagcgg cgtgcatacc tttccggcgg tgctgcaaag cagcggcctg      540
tatagcctga gcagcgttgt gaccgtgccg agcagcagct taggcactca gacctatatt      600
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<210> 299
<211> 666
<212> DNA
<213> Homo sapiens

<400> 299

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cctgggaagg gtctcgagtg gatgggcatt atttatccgg gcgatagcga tacccgttat      180
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<210> 300
<211> 657
<212> DNA

<213> Homo sapiens

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gccctgggct gcctggttaa agattatttc ccggaaccag tcaccgtgag ctggaacagc 480
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aacgtgaacc ataaaccgag caacaccaaa gtggataaaa aagtggaacc gaaaagc 657

<210> 301
<211> 663
<212> DNA
<213> Homo sapiens

<400> 301
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gcgcagaagt ttcagggccg ggtgaccatt accgcggatg aaagcaccag caccgcgtat 240
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attccttatc atctttttga ttattggggc caaggcaccc tggtgacggt tagctcagcg 360
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atttgcaacg tgaaccataa accgagcaac accaaagtgg ataaaaaagt ggaaccgaaa 660
agc 663

<210> 302
<211> 669
<212> DNA
<213> Homo sapiens

<400> 302
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acctatattt gcaacgtgaa ccataaaccg agcaacacca aagtggataa aaaagtggaa 660
ccgaaaagc 669

<210> 303
<211> 657
<212> DNA
<213> Homo sapiens

<400> 303
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tatattggtt atgatttttg ggccaaggc accctggtga cggttagctc agcgtcgacc 360
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ggggcgctga ccagcggcgt gcatacctttt ccggcggtgc tgcaaagcag cggcctgtat 540
agcctgagca gcgttgtgac cgtgccgagc agcagcttag gcactcagac ctatatttgc 600
aacgtgaacc ataaaccgag caacaccaaa gtggataaaa aagtggaacc gaaaagc 657

<210> 304
<211> 654
<212> DNA
<213> Homo sapiens

<400> 304
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gcgcagaagt ttcagggccg ggtgaccatt accgcggatg aaagcaccag caccgcgtat 240
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tggtatatgg attattgggg ccaaggcacc ctggtgacgg ttagctcagc gtcgaccaaa 360
ggtccaagcg tgtttccgct ggctccgagc agcaaaagca ccagcggcgg cacggctgcc 420
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ctgagcagcg ttgtgaccgt gccgagcagc agcttaggca ctcagaccta tatttgcaac 600
gtgaaccata aaccgagcaa caccaaagtg gataaaaaag tggaaccgaa aagc 654

<210> 305
<211> 666
<212> DNA
<213> Homo sapiens

<400> 305
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tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240
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cctgaggatc ttatttattt tgattattgg ggccaaggca ccctggtgac ggttagctca 360
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ggcctgtata gcctgagcag cgttgtgacc gtgccgagca gcagcttagg cactcagacc 600
tatatttgca acgtgaacca taaaccgagc aacaccaaag tggataaaaa agtggaaccg 660
aaaagc 666

<210> 306
<211> 687
<212> DNA
<213> Homo sapiens

<400> 306
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acctgtgcga tttccggaga tagcgtgagc agcaacagcg cggcgtggaa ctggattcgc 120
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cagtttagcc tgcaactgaa cagcgtgacc ccggaagata cggccgtgta ttattgcgcg 300
cgttggatga ctcctcctgg tcattattat ggttatactt ttgatgtttg gggccaaggc 360
accctggtga cggttagctc agcgtcgacc aaaggtccaa gcgtgtttcc gctggctccg 420
agcagcaaaa gcaccagcgg cggcacggct gccctgggct gcctggttaa agattatttc 480
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agcagcttag gcactcagac ctatatttgc aacgtgaacc ataaaccgag caacaccaaa 660
gtggataaaa aagtggaacc gaaaagc 687

<210> 307
<211> 669
<212> DNA
<213> Homo sapiens

<400> 307
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agctgcaaag gttccggata ttcctttacg agctattgga ttggctgggt gcgccagatg 120
cctgggaagg gtctcgagtg gatgggcatt atttatccgg gcgatagcga tacccgttat 180
tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240
cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgtcttcgt 300
gttcatgatt atgctatgta ttttgatctt tggggccaag gcaccctggt gacggttagc 360
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agcggcctgt atagcctgag cagcgttgtg accgtgccga gcagcagctt aggcactcag 600
acctatattt gcaacgtgaa ccataaaccg agcaacacca aagtggataa aaaagtggaa 660
ccgaaaagc 669

<210> 308
<211> 672
<212> DNA
<213> Homo sapiens

<400> 308
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agctgcaaag gttccggata ttcctttacg agctattgga ttggctgggt gcgccagatg    120
cctgggaagg gtctcgagtg gatgggcatt atttatccgg gcgatagcga tacccgttat    180
tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat    240
cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttttgtt    300
tcttataatg gttctgttcc ttattttgat tattggggcc aaggcaccct ggtgacggtt    360
agctcagcgt cgaccaaagg tccaagcgtg tttccgctgg ctccgagcag caaaagcacc    420
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agcagcggcc tgtatagcct gagcagcgtt gtgaccgtgc cgagcagcag cttaggcact    600
cagacctata tttgcaacgt gaaccataaa ccgagcaaca ccaaagtgga taaaaaagtg    660
gaaccgaaaa gc                                                        672
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<210> 309
<211> 666
<212> DNA
<213> Homo sapiens

<400> 309
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cctgggaagg gtctcgagtg gatgggcatt atttatccgg gcgatagcga tacccgttat    180
tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat    240
cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgtattatt    300
ggtgattatg ttattttttt tgatgtttgg ggccaaggca ccctggtgac ggttagctca    360
gcgtcgacca aaggtccaag cgtgtttccg ctggctccga gcagcaaaag caccagcggc    420
ggcacggctg ccctgggctg cctggttaaa gattatttcc cggaaccagt caccgtgagc    480
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ggcctgtata gcctgagcag cgttgtgacc gtgccgagca gcagcttagg cactcagacc    600
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aaaagc                                                               666
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<210> 310
<211> 609
<212> DNA
<213> Homo sapiens

<400> 310
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atgcctggga agggtctcga gtggatgggc attatttatc cgggcgatag cgatacccgt    120
tattctccga gctttcaggg ccaggtgacc attagcgcgg ataaaagcat tagcaccgcg    180
tatcttcaat ggagcagcct gaaagcgagc gatacggcca tgtattattg cgcgcgtctt    240
tttacttatc cttttcttta ttttgatgtt tggggccaag gcaccctggt gacggttagc    300
tcagcgtcga ccaaaggtcc aagcgtgttt ccgctggctc cgagcagcaa aagcaccagc    360
ggcggcacgg ctgccctggg ctgcctggtt aaagattatt tcccggaacc agtcaccgtg    420
agctggaaca gcggggcgct gaccagcggc gtgcatacct ttccggcggt gctgcaaagc    480
agcggcctgt atagcctgag cagcgttgtg accgtgccga gcagcagctt aggcactcag    540
acctatattt gcaacgtgaa ccataaaccg agcaacacca aagtggataa aaaagtggaa    600
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ccgaaaagc 609

<210> 311
<211> 666
<212> DNA
<213> Homo sapiens

<400> 311
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aaaagc 666

<210> 312
<211> 645
<212> DNA
<213> Homo sapiens

<400> 312
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tcgtgtacgg gtactagcag cgatgtgggc ggctataact atgtgagctg gtaccagcag 120
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<210> 313
<211> 645
<212> DNA
<213> Homo sapiens

<400> 313
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<210> 314
<211> 645
<212> DNA
<213> Homo sapiens

<400> 314
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catgagggga gcaccgtgga aaaaaccgtt gcgccgactg aggcc 645

<210> 315
<211> 638
<212> DNA
<213> Homo sapiens

<400> 315
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tcgtgtacgg gtactagcag cgatgtgggc ggctataact atgtgagctg gtaccagcag 120
catcccggga aggcgccgaa actgatgatt tatgatgtga gcaaccgtcc ctcaggcgtg 180
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catgagggga gcaccgtgga aaaaaccgtt gcgccgac 638

<210> 316
<211> 645
<212> DNA
<213> Homo sapiens

<400> 316
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catcccggga aggcgccgaa actgatgatt tatgatgtga gcaaccgtcc ctcaggcgtg     180
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caagcggaag acgaagcgga ttattattgc cagagctatg actttgttcg ttttatggtg     300
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<210> 317
<211> 638
<212> DNA
<213> Homo sapiens

<400> 317
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catcccggga aggcgccgaa actgatgatt tatgatgtga gcaaccgtcc ctcaggcgtg     180
agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg     240
caagcggaag acgaagcgga ttattattgc cagagctatg acttttataa gtttaatgtg     300
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gcgggagtgg agaccaccac accctccaaa caaagcaaca acaagtacgc ggccagcagc     540
tatctgagcc tgacgcctga gcagtggaag tcccacagaa gctacagctg ccaggtcacg     600
catgagggga gcaccgtgga aaaaaccgtt gcgccgac                            638
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<210> 318
<211> 638
<212> DNA
<213> Homo sapiens

<400> 318
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catcccggga aggcgccgaa actgatgatt tatgatgtga gcaaccgtcc ctcaggcgtg     180
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caagcggaag acgaagcgga ttattattgc cagagctatg actttcgtcg tttttctgtg     300
tttggcggcg gcacgaagtt aaccgttctt ggccagccga aagccgcacc gagtgtgacg     360
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agcgactttt atccgggagc cgtgacagtg gcctggaagg cagatagcag ccccgtcaag     480
gcgggagtgg agaccaccac accctccaaa caaagcaaca acaagtacgc ggccagcagc     540
tatctgagcc tgacgcctga gcagtggaag tcccacagaa gctacagctg ccaggtcacg     600
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<210> 319
<211> 642
<212> DNA
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<213> Homo sapiens

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cccgggacgg cgccgaaact gctgatttat gataacaacc agcgtccctc aggcgtgccg 180
gatcgtttta gcggatccaa aagcggcacc agcgcgagcc ttgcgattac gggcctgcaa 240
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gacttttatc cgggagccgt gacagtggcc tggaaggcag atagcagccc cgtcaaggcg 480
ggagtggaga ccaccacacc ctccaaacaa agcaacaaca agtacgcggc cagcagctat 540
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gaggggagca ccgtggaaaa aaccgttgcg ccgactgagg cc 642

<210> 320
<211> 639
<212> DNA
<213> Homo sapiens

<400> 320
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agcctgacgc ctgagcagtg gaagtcccac agaagctaca gctgccaggt cacgcatgag 600
gggagcaccg tggaaaaaac cgttgcgccg actgaggcc 639

<210> 321
<211> 672
<212> DNA
<213> Homo sapiens

<400> 321
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ggtctgagca gcccggtgac taaatctttt aatcgtggcg aggcctgata agcatgcgta 660

ggagaaaata aa 672

<210> 322
<211> 642
<212> DNA
<213> Homo sapiens

<400> 322
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cccgggacgg cgccgaaact gctgatttat gataacaacc agcgtccctc aggcgtgccg 180
gatcgtttta gcggatccaa aagcggcacc agcgcgagcc ttgcgattac gggcctgcaa 240
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ggagtggaga ccaccacacc ctccaaacaa agcaacaaca agtacgcggc cagcagctat 540
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gaggggagca ccgtggaaaa aaccgttgcg ccgactgagg cc 642

<210> 323
<211> 633
<212> DNA
<213> Homo sapiens

<400> 323
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caggcgccag ttctggtgat ttatgatgat tctgaccgtc cctcaggcat cccggaacgc 180
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accaccacac cctccaaaca aagcaacaac aagtacgcgg ccagcagcta tctgagcctg 540
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accgtggaaa aaaccgttgc gccgactgag gcc 633

<210> 324
<211> 633
<212> DNA
<213> Homo sapiens

<400> 324
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caggcgccag ttctggtgat ttatgatgat tctgaccgtc cctcaggcat cccggaacgc 180
tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240
gacgaagcgg attattattg ccagagctat gactttaatt ttcatgtgtt tggcggcggc 300
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ccgggagccg tgacagtggc ctggaaggca gatagcagcc ccgtcaaggc gggagtggag 480
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accgtggaaa aaaccgttgc gccgactgag gcc 633

<210> 325
<211> 648
<212> DNA
<213> Homo sapiens

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<210> 326
<211> 639
<212> DNA
<213> Homo sapiens

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<213> Homo sapiens

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tcgtgtagcg gcagcagcag caacattggc agcaactatg tgagctggta ccagcagttg 120

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<210> 328
<211> 645
<212> DNA
<213> Homo sapiens

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<210> 329
<211> 648
<212> DNA
<213> Homo sapiens

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<210> 330
<211> 642
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<213> Homo sapiens

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<211> 645
<212> DNA
<213> Homo sapiens

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<211> 645
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<210> 334
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<212> DNA
<213> Homo sapiens

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<213> Homo sapiens

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<210> 338
<211> 636
<212> DNA
<213> Homo sapiens

<400> 338
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ccgagcagcg aagaattgca ggcgaacaaa gcgaccctgg tgtgcctgat tagcgacttt     420
tatccgggag ccgtgacagt ggcctggaag gcagatagca gccccgtcaa ggcgggagtg     480
gagaccacca caccctccaa acaaagcaac aacaagtacg cggccagcag ctatctgagc     540
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<210> 339
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<212> DNA
<213> Homo sapiens

<400> 339

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<210> 340
<211> 648
<212> DNA
<213> Homo sapiens

<400> 340

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catcccggga aggcgccgaa actgatgatt tatgatgtga gcaaccgtcc ctcaggcgtg     180
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agctatctga gcctgacgcc tgagcagtgg aagtcccaca gaagctacag ctgccaggtc     600
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<210> 341
<211> 636
<212> DNA
<213> Homo sapiens

<400> 341

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<210> 342
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<212> DNA
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<213> Homo sapiens

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<212> DNA
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<212> DNA
<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

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<211> 633
<212> DNA
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<212> DNA
<213> Homo sapiens

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<210> 356
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1 5 10

<210> 357
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<212> PRT
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<400> 357
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Gly

<210> 358
<211> 17
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<400> 358
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<400> 359
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<210> 360
<211> 5
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<213> Homo sapiens

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Trp Phe Asp His
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Trp Phe Asp Val
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Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/086085 A3

(54) Title: HUMAN TIMP-1 ANTIBODIES

(57) Abstract: Human antibodies that bind to TIMP-1 can be used as reagents to diagnose and treat disorders in which TIMP-1 is elevated, such as liver fibrosis, alcoholic liver disease, cardiac fibrosis, acute coronary syndrome, lupus nephritis, glomerulosclerotic renal disease, benign prostate hypertrophy, colon cancer, lung cancer, and idiopathic pulmonary fibrosis.

INTERNATIONAL SEARCH REPORT	International application No. PCT/US02/12801

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07K 16/00, 16/40
US CL : 530/388.26, 389.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 530/388.26, 389.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST, STN, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GUEDEZ et al. In vitro suppression of programmed cell death of B cells by tissue inhibitor of metalloproteinases-1. Journal of Clinical Investigation, December 1998, Vol. 102, No. 11, pages 2002-2010.	1-2,4-9, 23-24, 26 and 28
A	HOLTON-ANDERSEN et al. Measurement of the noncomplexed free fraction of tissue inhibitor of metalloproteinases 1 in plasma by immunoassay. Clinical Chemistry. August 2002, Vol. 48, No. 8, pages 1305-1313.	1-2,4-9, 23-24, 26 and 28

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 September 2002 (18.09.2002)	12 DEC 2002
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. 703 305-3230	Authorized officer Maher M. Haddad Felicia D. Robert for Telephone No. 703 308-0196

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/12801

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-2, 4-9, 23-24, 26 and 28

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

I. Claims 1, 2, 4-9, 23, 24, 26, and 28 drawn to a purified preparation of a human antibody, human TIMP-1 comprising VHCDR3 of SEQ ID NO:1, VLCDR3 of SEQ ID NO: 44 or both amino acid sequence pair of SEQ ID NO:1 and SEQ ID NO: 44.

II Claims 1, 10-15, 23, 27 and 28, drawn to a purified preparation of a human antibody, rat TIMP-1 comprising VHCDR3 of SEQ ID NO:1, VLCDR3 of SEQ ID NO: 44 or both amino acid sequence pair of SEQ ID NO:1 and SEQ ID NO: 44.

III. Claims 1,3, 23, 25 drawn to a purified preparation of a human antibody, rat TIMP-13 comprising VHCDR3 of SEQ ID NO:1, VLCDR3 of SEQ ID NO: 44 or both amino acid sequence pair of SEQ ID NO:1 and SEQ ID NO: 44.

IV-CVIII. Claims 16-22, drawn to a purified preparation of a human antibody, TIMP-1 comprising VHCDR3 of SEQ ID NO:1-43, 360 and 140-182, VLCDR3 of SEQ ID NO: 44-86, 365-379, 97-139 or both amino acid sequence pair set forth in claims 18, 19, or 22, respectively.

CIX- CCXV Claims 29-52, drawn to a purified polynucleotide enoding VHCDR3 of SEQ ID NO:1-43, 360 and 140-182, VLCDR3 of SEQ ID NO: 44-86, 365-379, 97-139 or both amino acid sequence pair set forth in claims 18, 19, or 22, respectively, vectors and host cells.

CCXVI-CCLXVIII. Claims 54-63 , drawn to a method of decreasing an MMP-inhibiting activity of a TIMP-1, wherein SEQ ID NO pair as set forth in claim 63, respectively.

CCLXVIII-CCCXXI Claims 64-68, drawn to a method of ameliorating symptoms of a disorder, wherein SEQ ID NO pair as set forth in claim 68, respectively.

CCCXXII- CCCLXXIV. Claims 69-72, drawn to a method of detecting a TIMP-1, wherein SEQ ID NO pair as set forth in claims 72, respectively.

CCCLXXV-CDXXVII. Claims 73-78, drawn to a method to aid in diagnosing a disordr, wherein SEQ ID NO pair as set forth in claim 76, respectively.

The inventions listed as Groups I-CDXXVII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The special technical feature of Group I is a purified preparation of a human antibody, TIMP-1 comprising VHCDR3 of SEQ ID NO:1, VLCDR3 of SEQ ID NO:44 or both amino acid sequence pair of SEQ ID NO:1 and SEQ ID NO:44.

The special technical feature of Group II, drawn to a purified preparation of a human antibody, rat TIMP-1 comprising VHCDR3 of SEQ ID NO:1, VLCDR3 of SEQ ID NO: 44 or both amino acid sequence pair of SEQ ID NO:1 and SEQ ID NO: 44.

The special technical feature of Group III, drawn to a purified preparation of a human antibody, rat TIMP-13 comprising VHCDR3 of SEQ ID NO:1, VLCDR3 of SEQ ID NO: 44 or both amino acid sequence pair of SEQ ID NO:1 and SEQ ID NO: 44.

The special technical feature of Groups IV-CVIII, drawn to a purified preparation of a human antibody, TIMP-1 comprising VHCDR3 of SEQ ID NO:1-43, 360 and 140-182, VLCDR3 of SEQ ID NO: 44-86, 365-379, 97-139 or both amino acid sequence pair set forth in claims 18, 19, or 22, respectively.

The special technical feature of Groups CIX-CCXV, drawn to a purified polynucleotide enoding VHCDR3 of SEQ ID NO:1-43, 360 and 140-182, VLCDR3 of SEQ ID NO: 44-86, 365-379, 97-139 or both amino acid sequence pair set forth in claims 18, 19, or 22, respectively, vectors and host cells.

The special technical feature of Groups CCXVI-CCLXVII, drawn to a method of decreasing an MMP-inhibiting activity of a TIMP-1, wherein SEQ ID NO pair as set forth in claim 63, respectively.

The special technical feature of Groups CCLXVIII-CCCXXI, drawn to a method of ameliorating symptoms of a disorder, wherein SEQ ID NO pair as set forth in claim 68, respectively.

The special technical feature of Groups CCCXXII- CCCLXXIV, drawn to a method of detecting a TIMP-1, wherein SEQ ID NO pair as set forth in claims 72, respectively.

The special technical feature of Groups CCCLXXV-CDXXVII, drawn to a method to aid in diagnosing a disordr, wherein SEQ ID NO pair as set forth in claim 76, respectively.

Accordingly, Groups I-CDXXVII are not so linked by the same or a corresponding special technical feature within meaning of PCT Rule 13.2 so as to form a single general inventive concept.

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